FMRI OF LANGUAGE OUTPUT: CONCEPTUAL PRIMING AND PRACTICE

By

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This dissertation is dedicated to my parents, Margaret and George Sadek.

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Priming is a form of implicit memory that results in facilitation of behavior without conscious awareness. Priming is frequently intact in patients who are otherwise unable to consciously recall recently learned information. Priming of single words can occur by emphasizing the physical aspects of the words or by emphasizing the semantic aspects of the words, (perceptual and conceptual priming). The theory of transfer appropriate processing suggests that priming is due to the overlap in cognitive processes between the study phase and the test phase of priming experiments. Recent functional neuroimaging studies have suggested that priming may cause a reduction in neural energy needs related to facilitated access to primed information. Perceptual priming is associated with activation reduction in areas of cortex known to be involved in perceptual processing, while conceptual priming results in activation reduction in areas of cortex thought to be involved in semantic processing.

Two experiments were designed to explore whether conceptual priming of category exemplar generation can result in activation reductions in left lateral and left

medial frontal cortex, which are involved in semantic processing and response selection/production respectively. In Experiment 1, participants performed a word-cued semantic association task that required them to produce a word that was semantically related to the cue word. Target responses came from nine semantic categories. Priming was assessed with a category exemplar generation test including nine primed and nine unprimed categories. Results confirmed that this method effectively produced priming. In Experiment 2, the same priming task was performed during functional magnetic resonance imaging (FMRI). The hypothesized reductions in activation were not observed in medial or lateral left frontal cortex. The limitations of the design are discussed, including the insensitivity of the design to the relatively small effect size. A secondary task assessed whether practicing category exemplar generation would result in activation reductions in left medial and left lateral frontal cortex. While practicing category exemplar generation resulted in a behavioral change, no change in medial or lateral frontal activity was observed. Rather, posterior cingulate and medial parietal cortex that initially exhibited rest-related activity showed a mitigation of this activity as the task became more familiar. This change was interpreted to reflect a change in attentional states as the generation task became more familiar.

CHAPTER 1
LANGUAGE AND PRIMING

Priming is a change in the ability to recognize or produce an item as a result of prior exposure to the item. It is a form of implicit memory, which is the nonconscious influence of past experience on current behavior (Schacter & Buckner, 1998b). Implicit memory is a concept that dates back to the mid 1800s, when Descartes referred to the unconscious impact of aversive experience on a child that lasted long after the conscious memory of the event (Schacter, 1987). While several philosophers have discussed the idea of memory without awareness, the first systematic empirical study of implicit memory occurred in the late 1800s. Several lines of research addressed memory without awareness, including the neurological research of Sergei Korsakoff regarding preserved learning in amnesic patients, the psychiatric research of Pierre Janet and Sigmund Freud on the unconscious expression of prior trauma, the experimental psychological research of Ebbinghaus regarding his retention of information that he could not recall learning, and the psychical observations that crystal gazing and automatic writing (writing performed while under a hypnotic trance) were simply unconscious expressions of prior experiences. Contemporary technology has simplified research on implicit memory and allowed a proliferation of studies. This dissertation will review some of the research in priming with the ultimate goal of testing the hypothesis that a specific form of priming (priming in category exemplar generation) can be studied with contemporary brain imaging technology to reveal information about the biological basis of priming. This

dissertation also will review some of the research in the area of skill development to explore the overlap in brain areas affected by both priming and practice.

Cognitive Neuropsychological Model of Language

Priming of linguistic material is based on the assumption that language is organized in a particular fashion, particularly with respect to the existence of a semantic system. The experiments in the present study are based on the cognitive neuropsychological theory of language proposed by Ellis and Young (1988). This model is depicted in Figure 1. This model states that language is initially comprehended through the auditory analysis system, through which the various sounds contained within words (e.g., ke-'ner-ē for "canary") are determined to be speech. Once the sounds are determined to be speech, they are compared to the known set of words to determine which word is being heard. This known set of words is called the phonological input lexicon and contains all the auditory forms of words that a person knows. After a particular speech pattern has been identified as a word, the meaning of the word is activated in the semantic system, and the word is comprehended.

Language output occurs after the intention to speak has developed. Suppose a person wants to say the word CANARY. The speaker has chosen his intended meaning from within the semantic system, in this case a small yellow bird. Correct selection of the appropriate semantic concept is ensured, since each concept has its own unique representation in the semantic system no matter how subtly it differs from other concepts. For example, if you are trying to say the word CANARY, it is likely that similar words will arise as possible choices in your language output system, such as COCKATIEL, PARAKEET or even BIRD. The semantic system ensures that CANARY is chosen since

it is the only candidate that possesses all the attributes of being small, yellow, and a domestic bird.

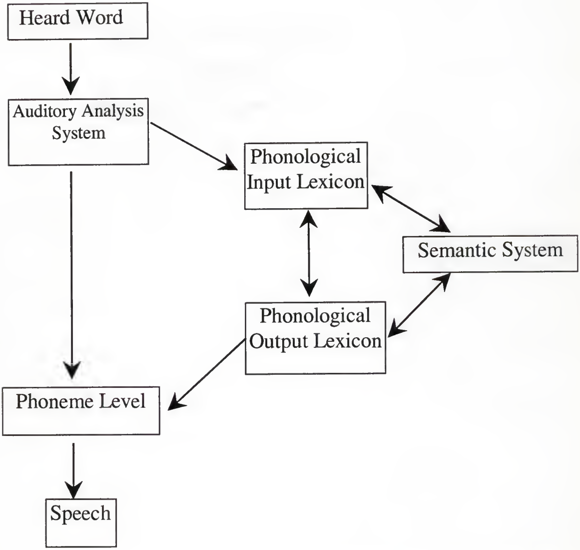


Figure 1. Cognitive neuropsychological model of language proposed by Ellis and Young (1988).

The concepts from the semantic system are then matched with the appropriate spoken form of the word, in this case /ke-'ner-ē/. The collection of all spoken word forms is called the phonological output lexicon. The exact mechanism of the translation from meaning to spoken form will be assumed to be the activation of specific phoneme

"nodes" by the phonological output lexicon (Ellis & Young, 1988). Thus, the phonological output lexicon is a channel through which the phonemes that comprise a particular word are activated and associated with the intended meaning from the semantic system. When the specific phonemes have been selected, the motor system is engaged and speech occurs. While the actual speech output lexicon is more complicated (e.g., supporting suffixes, prefixes, grammar; see Levelt, 1989), we will focus at the single word level only in the set of experiments in this dissertation.

Priming: Definition and Review

The language system is based on the fact that information about the world is stored somewhere in the brain in a memory system. One such system has been called "declarative" (or "explicit") memory and has been defined as the ability to recall previously learned information (Squire, 1992). According to Squire (1992), these terms are actually defined by their dependence on a particular system in the brain, such that when that system fails, so does declarative memory. In addition, many forms of memory occur without requiring conscious awareness of the act of recollection. There are unconscious influences on what we think and say, such as the experience of having a song or idea in mind without being aware that it was recently encountered somewhere else. This is an example of priming, whereby a prior experience facilitated the re-occurrence of that experience without awareness that the facilitation occurred. Priming has been demonstrated reliably in the laboratory, as in the study by Hamann (1990). He had participants say how much they liked certain words. They were subsequently more inclined to produce those words at a later time when given a category-cued association

task. This is called priming of category exemplar generation (CEG), and it is a form of implicit memory.

As mentioned above, memory can be divided into explicit or implicit domains (Squire, 1992; Schacter & Tulving, 1994; Graf & Schacter, 1985). Explicit memory is memory that requires conscious recollection of previous knowledge or experiences (Graf & Schacter, 1985), such as remembering your address or where you left your keys. Explicit memory can be contrasted with implicit memory, which is the re-experiencing of past knowledge or events without awareness that prior knowledge or events are being re-experienced. There are several subdivisions within implicit memory. One type of implicit memory is procedural memory, such as tying one's shoes. Another type of implicit memory is priming, which can be defined as a increase in the ability to recognize or produce an item as a result of prior exposure to the item (Schacter & Buckner, 1998b). All forms of memory, including priming, require at least two stages: (1) encoding, during which the information is entered into the memory system, and (2) recollection, during which the encoded information is "re-collected" or experienced again in some fashion. Most studies of priming have two phases: the encoding or study phase, in which the information is first encountered and processed; and the test phase, when the information is either recalled or encountered again without reference to the study phase. For example, if you recently read the word "rock" and you are asked later to make a word that starts with the letters "ro_ _," you are more likely to produce the word "rock." Such a task is called word stem completion priming, since the first part of the word (the "stem") is provided during the test phase. Priming is a form of memory, since past

experience affects future behavior, and priming that involves linguistic material relies on mechanisms of the language system such as the one proposed by Ellis and Young (1988).

Characteristics of Priming

Priming has been explored extensively, and many of its characteristics are well described (Graf & Masson, 1993; Lewandowsky, Dunn, & Kirsner, 1993; Schacter & Buckner, 1998b). One characteristic of priming, as mentioned above, is that priming occurs without conscious effort at recollection. Conscious recollection here is defined as intentional reference back to the learning episode during the memory test (Schacter, Bowers, & Booker, 1989). Patients with amnesia perform poorly on tasks that require conscious recollection of recent past experiences. For example, Warrington and Weiskrantz (1974) tested patients with amnesia on the stem completion priming task. The patients, whose yes/no recognition memory was impaired, performed similarly to the non-amnesic control subjects on the priming task. Thus, when the requirement of conscious recollection is removed, amnesic patients can perform at a near normal level on stem completion priming as well as on many other priming tasks (e.g., Warrington & Weiskrantz, 1970, 1974; Graf, Squire, & Mandler, 1984). These experiments provided strong evidence for the case that behavior can be influenced without awareness.

Priming always involves the facilitation of a response. Facilitation can be measured through various test methods (Brown & Mitchell, 1994). For example, a primed response can be elicited by a word stem, a word fragment (e_g_e for *eagle*), a word-cued association (table – chair), a category-cued association (name an article of clothing), or a general knowledge question (What is the fastest animal on earth?). Facilitation also can be measured through faster response times on tasks such as word

reading, lexical decision (Is this a real word?), category verification (Is this a fruit?), or abstract/concrete judgment. The task of interest in the present study is category-cued association, or more specifically, category exemplar generation (CEG) priming.

A final characteristic of priming is that facilitation can occur through at least two mechanisms: through the physical properties or through the meaning of the primed material (Brown & Mitchell, 1994). These two mechanisms of priming have been called data-driven (or perceptual) and conceptually-driven (or conceptual) processing (Roediger, 1990; Jacoby, 1983). If you were asked to identify a word that was presented to you, such as "rock," you would be faster to identify the word if it was printed in the same typeface as before. This is perceptual priming. Similarly, if you had just seen another word that was related to "rock," (such as "boulder"), you would be faster to identify the word "rock." This is conceptual priming. In both cases, your response has been facilitated by a previous experience, though for different reasons. In the first case, facilitation occurred because of prior processing of the physical characteristics of the word. In the second case, facilitation occurred because of the prior processing of semantic characteristics related to the word.

The main purpose of the present study is to identify important brain regions affected by CEG priming. CEG priming is seen when subjects are biased toward particular items when asked to list items from a given category. The theoretical basis of these experiments must account for priming based on semantic processing. A leading model that accounts for CEG priming is Transfer Appropriate Processing (TAP; Morris, Bransford & Franks, 1977; Roediger, 1990) and will be reviewed below.

Transfer Appropriate Processing

Transfer appropriate processing (TAP; Morris, Bransford, and Franks, 1977) proposes that memory performance depends on the degree of overlap between cognitive processes applied during study and during test. TAP was initially devised to explain weaknesses in the levels of processing theory, which proposed that memory performance was better with "deeper" encoding of information (e.g., meaning-based encoding) than with shallow encoding (e.g., based on physical characteristics). Morris, Bransford, and Franks (1977) provided data to suggest that memory performance did not always improve with deeper encoding. Instead, they suggested that memory performance was more influenced by the match in contexts between study and test. For example, if both study and test involved focusing on the physical aspects of a word, such as whether it rhymed with a given word, memory performance would be better than if the study task involved primarily rhyming and the test involved primarily a focus on word meaning. Morris, Bransford, & Franks (1977) presumed that the mechanism was an enhancement of the memory "trace" due to the re-utilization of the same processes at test that were utilized during study. In our example, the trace connecting the studied word and the test word was stronger if both study and test focused on phonological features. TAP applies to many priming paradigms besides word priming, including priming of degraded pictures (Weldon & Roediger, 1987; Warrington & Weiskrantz, 1968) and picture naming (Durso & Johnson, 1979).

TAP was eventually modified to explain the differences between explicit and implicit memory (Roediger, 1990; Blaxton, 1989; Roediger & Srinivas, 1993). With a slight name change, Roediger (1990) outlined an approach named "transfer-appropriate procedures," which incorporates TAP into a theory to explain the apparent advantage of

semantic encoding in explicit memory and perceptual encoding in priming. Roediger (1990) outlined four main assumptions. First, memory performance depends on the overlap in cognitive operations between study and test. Second, most implicit and explicit memory tests typically require different retrieval operations and, as a result, benefit from the engagement of different processes of encoding. Therefore, implicit and explicit memory are somewhat independent since they rely on different retrieval operations. This dissociation is described in the third assumption, which states that most explicit memory tests rely on the processing of meaning, thus benefiting maximally from semantically based encoding. And fourth, most implicit memory tests rely on processing of perceptual features and, as a result, benefit maximally from perceptually based encoding. Jacoby (1983) referred the explicit-implicit differences in terms of "conceptually-driven tests" and "data-driven tests." Conceptually driven tests are those that rely primarily on semantic processing and that are most typically used to assess explicit memory. Data-driven tests are those that rely primarily on perceptual operations and are most typically used to assess implicit memory (Jacoby, 1983). It is important to note that the "transfer-appropriate procedures" explanation was an attempt to account for dissociations among different types of experimental memory tests, and the theory was not intended to explain the true nature of implicit and explicit memory.

In contemporary terms of neural networks, access to the primed item is made easier by the higher activation level of that item as a direct result of the act of recent access to the item. Graf and Gallie (1992) described the process as follows. A unit on the neural network (analogous to the "node" as discussed above in the language model of Ellis and Young, 1988) becomes established when there is mutual activation of the

various neurons through their interconnections. The study task effectively establishes a unit by accessing the item through a set of neural connections. At a later time, the unit is more likely to become activated again even if only part of the unit was activated the second time around. In other words, access to the word "rock" through a semantic association, such as "Gibraltar," will elevate the activation level of the entire unit that represents the meaning of "rock." If a later cognitive process engages the semantic system related to "rock" (e.g., "list everything that sinks in water"), the word "rock" is more likely to become activated and to be chosen as a response. The present study focuses on conceptually-driven priming as termed by TAP. For the sake of historical review and to establish the notion of facilitation, perceptual priming will be discussed first.

Perceptual Priming

Much of the theoretical basis of priming comes from perceptual priming research (Roediger & Srinivas, 1993; Masson & Freedman, 1990; Ratcliff & McKoon, 1997). With regard to single-word processing, there are three main techniques used to test to perceptual word processing. These include stem completion (e.g., "fro_ _"), word fragment completion (e.g., "e_g_le"), and word identification (e.g., word reading). Each of these priming tasks is sensitive to changes in the physical characteristics of words during study. For example, Rajaram & Roediger (1993) presented words in either a written, auditory, or pictorial format and later asked participants to perform a perceptual identification, word stem completion, or word fragment completion priming test that made no reference to the study task. Since the test format (word stem, word fragment, or perceptual identification) was always conducted in the written word modality, words that

were initially studied in the written format were more consistently identified or produced than words studied in other modalities. Thus, the degree of consistency between the study and test of the surface features of the words had the most influence on priming (Rajaram & Roediger, 1993). Some studies have showed that priming effects are sensitive to typefont (Roediger & Blaxton, 1987), and at least one study (Gardiner, Sutton, & Dawson, 1989) observed that priming was strongest when the same stimuli used in the test task (e.g., a word fragment, like b_ _ _e_or for "bachelor") was also used during study (e.g., *a single, unmarried man is a* b_ _ _e_or). Changes as small as the addition or omission of a single letter reduced the magnitude of priming significantly (Gardiner et al., 1989). Although the specific effects of minor variations in physical characteristics are still unclear, ample evidence supports the notion that both major and minor variations in physical characteristics can affect perceptual priming.

Conceptual Priming

Conceptual priming is unaffected by variations in physical characteristics, and it is usually thought to involve the transfer of semantic processing between study and test to produce priming effects. In studies of conceptual priming, priming is assessed with a test task that always involves some form of semantic processing, such as word knowledge question ("What is the capital of Italy?"), category exemplar generation ("Name as many fruits"), word-cued association ("table" – ch---), or picture naming (Brown & Mitchell, 1994). Although it is true that word forms can be accessed independently of the semantic system (Ellis & Young, 1988), the important aspect of these priming tests is that prior semantic processing facilitates the participants' performance independent of the processing of the word form. Prior semantic processing is achieved through focusing on

semantic characteristics during the study task. Because the test task in conceptual priming usually involves semantic processing, the magnitude of priming is consistently larger for words initially studied with semantic processing than for those studied with an emphasis on processing physical characteristics (Keane et al., 1997; Blaxton, 1992; Graf & Schacter, 1985; Hamann, 1990). The cause of the priming effect is hypothesized to be a higher activation level of the semantic representation of the item induced by previous semantic processing. When similar semantic processes are invoked again, the item is more accessible (e.g., faster to be recognized or more likely to be chosen as a response) because of its higher level of activation. In other words, its node on the semantic system is more easily activated.

Priming in Category Exemplar Generation

There are many ways to test conceptual priming, including general knowledge questions (Blaxton et al., 1992; Vaidya et al., 1996), category exemplar generation (CEG) priming (Gardner et al., 1973; Keane et al., 1997; Hamann, 1990), or word-cued association (Vaidya et al., 1995; Shimamura & Squire, 1984; Cermak, Verfaellie, & Chase, 1995). Although all are effective in producing priming, the task of interest for the present study is CEG priming. Category exemplar generation requires not only semantic processing but also other cognitive systems that support response production. As Vaidya et al. (1997) have suggested, conceptual priming involves a complex set of mechanisms. It is the goal of this dissertation to test the hypothesis that priming can affect not only the semantic system but also other systems that are engaged by CEG. In CEG priming, priming is manifested by an increased probability of generating a category exemplar that was previously studied. For example, a participant may have been asked to judge

whether words were abstract or concrete. Later, without the subject's awareness that their memory is being tested, they are asked to generate as many items from a given category as they can. Priming is measured by how many study words were produced. As illustrations, two studies using this methodology are reviewed below.

Hamann (1990) conducted an experiment in which participants either rated how much they liked each word (semantic study) or responded if two words in a row contained any common vowels (physical study). During the test phase, they were asked either with a general knowledge question, for which the answer was a studied word, or with CEG, for which several exemplars had been studied from a number of categories. Both of these test phase tasks were semantic in nature. Hamann hypothesized that the semantic study task would result in greater priming than the physical study for both types of test phase tasks due to the overlap in semantic processing. As expected, Hamann (1990) found that priming was greater for the semantic study task regardless of the type of test task. In addition, priming effects lasted at least 90 minutes.

Another study that used CEG priming was conducted by Keane et al. (1997). She tested the hypothesis that conceptual processing is primarily responsible for explicit memory performance by taking a group of patients with explicit memory impairment (limbic-diencephalic amnesics) and observing their performance on a task of conceptual priming (CEG priming). If conceptual processing is responsible for explicit memory, then patients who show explicit memory impairment should also show impairment on conceptual priming tasks as well. Participants studied a series of category exemplars through either a semantic study task (which required a judgment of whether each item was man-made or naturally occurring) or a perceptual study task (which required a

judgment of whether each word was in uppercase or lower case letters). Then, participants were asked to say aloud as many items from given categories as they could. Exemplars from some of the categories had been encountered during the study task. No reference to the studied words was made. The pattern of results was the same as that in the study by Hamann (1990): priming of category exemplar generation was greater with semantic study. Patients and controls produced about 8% more target items in categories for which exemplars had been encountered in the semantic study condition compared to approximately 3% more target items in the physical study condition. The authors concluded that explicit memory may not be so reliant on semantic processing.

As the studies by Keane et al. (1997) and Hamann (1990) demonstrate, CEG priming is reliable and is enhanced by semantic study. The mechanism of CEG priming has been assumed to be the transfer of semantic processes between study and test. The cognitive mechanisms will be explored in more detail next.

Mechanisms of Conceptual and Output Systems Priming

A word can be conceptualized as a representation that exists as a single unit or node in a network. When a word is spoken, its exact speech form (pronunciation of phonemes, or word sounds) is accessed in a different system from the semantic system (Ellis & Young, 1988). Let us assume that meaning can be accessed either through the perception of the word form (e.g., hearing a word) or through another concept related to the word. In our language model in Figure 1, the concept of "cat" can be accessed in the semantic system if the sounds /kat/ are heard or if another semantic representation related to "cat" is active, such as the concept of domestic animals. The proposed cognitive mechanisms for CEG priming are depicted in Figures 2 and 3.

The study task is represented in Figure 2. The study task is a word association task that includes both a semantic cue and a phonemic cue to the target response. A subject is asked to say a word that is related to the cue word and that begins with the

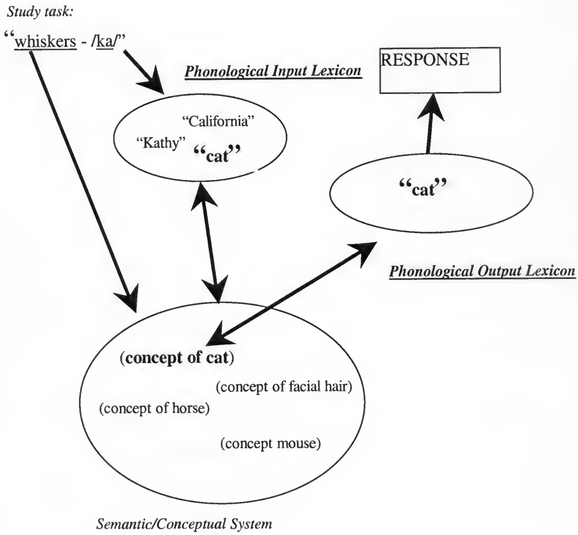


Figure 2. Cognitive mechanism of word-cued association.

given phonemic cue. This task involves the phonological input lexicon, the semantic system, and the phonological output lexicon. The test task is represented in Figure 3. A subject is asked to say as many words from the given category as he or she can. The test

task includes only a category cue from which exemplars were produced. This task involves only the semantic system and the phonological output lexicon.

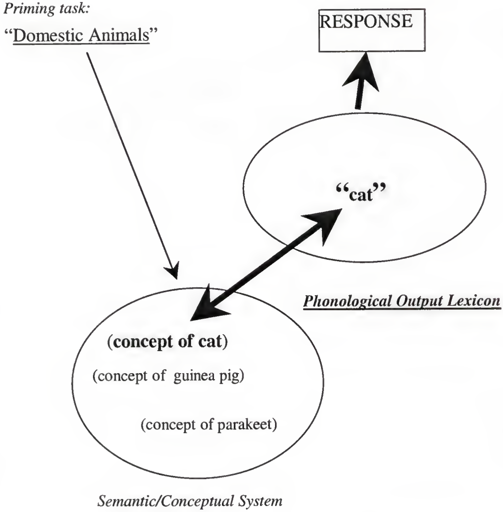


Figure 3. Cognitive mechanism of category exemplar generation priming. Dark arrows represent processes also engaged by study task in Figure 3 and represent primed processes.

In Figure 3, the dark arrows between the Semantic/Conceptual System, the Phonological Output Lexicon, and the Response represent the processes that overlap between study and test. The example is priming of the word "cat." The word "cat" becomes highly activated as a result of the study task. During the study task, the semantic system was

engaged and the response "cat" was chosen and produced. Activation of the word "cat" remained high, so that, during the test task, a second semantic system search (this time for domestic animals) resulted in the selection and production of the word "cat" due to its higher state of activation. If these tasks engage the specified cognitive operations (semantic processing and response selection and production), then areas of the brain that are involved in these processes are likely to show evidence of the facilitation.

CHAPTER 2
THE NEURAL BASIS OF PRIMING

Evidence Regarding Amnesia

Cognitive theories of memory such as the one described above have been influenced heavily by neuropsychological research into the biological basis of memory. The first discussions about the biological basis of implicit memory came from research on patients with amnesia (Schacter & Tulving, 1994; Squire, 1992). This theory of the dissociation between implicit and explicit memory came to be known as the systems theory. The central hypothesis of systems theory is that there are at least two memory systems supported by the human brain. Warrington and Weiskrantz presented early evidence for two separate memory systems in 1968. Amnesic patients participated in a stem completion priming task. They were asked to evaluate a set of words and then to complete a word (from which the final letters had been removed) with the first response that comes to mind. Amnesic patients performed relatively well on stem completion of studied words, in contrast to their impaired performance on tests of recall and recognition. This evidence of preserved implicit memory in patients who previously were seen as devoid of permanent memory has been replicated in many studies thereafter (e.g., Warrington & Weiskrantz, 1974; Graf & Schacter, 1985; Graf, Squire, & Mandler, 1984; Gardner et al., 1973; Keane et al., 1997). Preserved implicit memory in amnesia

formed the foundation of the argument for multiple memory systems. Because structures that are necessary for implicit memory must be preserved in amnesia, implicit memory must rely on a separate anatomical system. Most patients with amnesia suffer damage to the medial temporal lobe, including the hippocampus and/or the parahippocampal gyrus, to the diencephalic region, including the mammillary bodies, to basal forebrain structures including the nucleus basalis, the nucleus of the diagonal band, and/or the medial septal nucleus, and/or damage to specific thalamic nuclei (Squire, 1992; Damasio et al., 1985). Therefore, it was believed that explicit memory depended on some or all of these structures (Squire, 1992), whereas implicit memory depended on structures outside these systems.

What systems are responsible for the intact priming in amnesia? One perspective is that perceptual priming mechanisms are preserved in amnesia. The early research on preserved memory in amnesia can be interpreted to support preserved perceptual systems. Warrington and Weiskrantz (1970; 1974) used identification of degraded words to test implicit memory for words that were studied earlier. After the patients studied lists of words (without overt reference to a learning or memory task), they were asked to identify words that had been degraded (i.e., words with bits of the letters removed). They found, as in the stem completion priming study reported above, that amnesic patients could identify words that they had seen before sooner than those that were not studied in spite of poor explicit recall or recognition for studied words. Prior visual processing of the words allowed the patients with impaired conscious recollection to recognize words more quickly, presumably because the word was at a higher resting state of activation for coming into consciousness. Intact perceptual priming in amnesia has been replicated

many times (see Schacter & Buckner, 1998b for a review). However, the notions of an explicit/conceptual and an implicit/perceptual distinction as an explanation for intact priming in amnesia has been dispelled by research confirming that in many cases, conceptual priming is intact in amnesia, such as the study by Keane et al. (1997) described above. Researchers are turning to other techniques to learn about the systems of implicit memory, such as functional neuroimaging.

Evidence Regarding Functional Neuroimaging

Perceptual Systems

Buckner and colleagues (1995) provided data that identified specific neural systems involved in perceptual priming. If priming causes a change in patterns of brain activity, then knowledge about functional neuroanatomy can be used to provide novel and detailed information about the neural and theoretical basis of priming. Buckner et al. (1995) used functional neuroimaging to observe that brain areas related to perception are indeed involved in perceptual priming. This study, which included data reported by Squire et al. (1992), used Positron Emission Tomography (PET) to compare the functional neuroanatomy of explicit recall and word stem completion priming. Twenty-nine participants studied words semantically by rating how much they liked each word. The study words were presented either auditorily, in uppercase letters, or in lowercase letters. This sensory variation in stimulus presentation forms the perceptual basis of the task. The test phase required participants to complete 3-letter word stems, in all uppercase letters, with the first word that came to mind. The test task relied on processing of physical characteristic of words (three-letter stems) without requiring the use of word meaning, making it a perceptual task. There was no reference to the studied words,

making it an implicit memory paradigm. As a control task, the participants completed three-letter word stems that were unrelated to the study items. The focus of the study was to determine whether priming was different if the study words were presented in capital letters compared to lowercase letters. No semantic processing was required to complete the test phase. The authors found that the areas of the brain active during the control task included left prefrontal cortex, supplementary motor area (SMA), anterior cingulate, left superior and anterior temporal cortex, and medial dorsal thalamus. When priming was compared to the control condition, the priming task activated many of the same areas, but resulted in *less* blood flow than in the control task in three areas: white matter medial to the caudate nucleus (probably reflecting activity within the caudate nucleus, since white matter should not show functional activation; see Nadeau & Crosson, 1995), posterior insula, and bilateral occipitotemporal cortex. The reduction in blood flow was greater in right occipitotemporal cortex. The authors interpreted reduced blood flow in occipitotemporal cortex, known to be involved in visual word form processing (Petersen et al., 1988), as an indicator of more efficient visual processing of the word during the second exposure to the stimuli. The authors concluded that priming results in decreased blood flow to brain areas that are known to be involved in the task at hand, in this case visual processing of words. This decrease in blood flow suggests that more efficient behavioral performance in priming has correlates at a physiological level.

<u>Semantic and Output Systems</u>

Just as perceptual priming relies on perceptual brain systems (i.e., occipitotemporal cortex for visual features), conceptual priming should rely on brain systems that support semantic processing. Unfortunately, much less is known about

semantic brain systems than is known about perceptual systems. It has been demonstrated, however, that one form of conceptual priming impacts the lateral frontal lobe (in or around the cortex of Brodmann's areas (BA) 46, 47, 9, and/or 8), while perceptual priming does not (Schacter & Buckner, 1998b; Buckner et al., 1998; Demb et al., 1995; Gabrieli et al., 1996). Demb and colleagues (1995) used FMRI to observe a decrease in activation due to priming in the same fashion as Buckner et al. (1995). Demb and colleagues (1995) utilized conceptual priming rather than perceptual priming and observed a decrease in dorsolateral frontal activation. Six participants judged whether words were abstract or concrete while undergoing FMRI of selected regions of frontal cortex. Some words occurred only once during the scanning session, while other words occurred twice. The test phase therefore consisted of performing the same semantic judgment task as in the study phase. The authors noted a decrease in activation in the following areas when the same words were seen twice compared to when words were seen only once: left inferior frontal cortex (BA 45, 46, 47), and dorsolateral frontal cortex (BA 8). Since the same areas were not activated by a task that required judging physical characteristics of word (e.g., whether words were upper or lower case), the authors concluded that left inferior frontal cortex was involved in processing the meaning of words, and that repeated processing was more efficient as evidenced by the reduced activation in those areas. Gabrieli et al. (1996) used the same task on 16 participants and observed the same decrease in activation in inferior frontal cortex and, to a lesser extent, dorsal frontal cortex. Both studies concluded that conceptual priming could occur after a single exposure to a stimulus, and that reduced activation in priming was a result of increased processing efficiency.

Blaxton and colleagues (1996) attempted to demonstrate that there are separate neural systems supporting conceptual and perceptual memory. They conducted PET scans while participants performed both perceptual and conceptual implicit memory tasks. Prior to each scan, participants studied words either with a semantic strategy, in which they thought about how a pair of words were related, or with a perceptual study, in which they read single words aloud (though no additional effort was made to focus attention on perceptual features). Subjects underwent functional neuroimaging during the test phase. Different memory tests were performed for each study condition. For semantic study, participants were tested either with an explicit cued-recall format, in which participants would say the word that was previously paired with the cue word, or with an implicit association task, in which participants were to say the first word that came to mind while viewing the cue words. The control task, to which each of the implicit and explicit semantic recall images was compared, was production of a semantic associate to unstudied cues. Just as in the semantic study condition, participants in the perceptual study condition were tested with both explicit and implicit memory tests. The explicit test required the participant to complete a word fragment (e.g., E_G_E) with a word from the study phase. The implicit memory test required participants to complete word fragments with the first work that came to mind. The control task for nonsemantic memory tests was completion of word fragments that had not been studied. The authors compared images obtained during the implicit memory test to images obtained during the control task and observed decreases in activation associated with the conceptual implicit memory test were seen in left temporal (BAs 38, 42) and posterior cingulate (BA 31) regions. The authors did not explain the lack of an expected decrease in activation in

lateral frontal cortex observed in other studies of conceptual priming (Demb et al., 1995; Buckner et al., 1998). The explanation may lie in methodological problems, including the possibility that implicit memory was contaminated by explicit recall due to counterbalancing that placed explicit tasks before the implicit task half of the time, possibly resulting in continued explicit recall into the implicit task. Another methodological concern is that study task instructions were vague ("think about" how word pairs are related) and may have affected the transfer of processes by not controlling the specific processing engaged by each subject. These same methodological problems may also explain why there were numerous regions of *increased* activation during the conceptual priming test task, including left insular and left lateral frontal cortex (BA 9, 10, 47), since the cognitive processes used by the participants during the implicit tasks may not have been adequately controlled. The results of the perceptual implicit memory task were somewhat more convergent with previous research in that decreases in activation were observed in posterior cortex associated with visual perceptual processing (BA 17).

Anatomic Substrates of Conceptual Priming

Lateral frontal cortex

As noted earlier in this introduction, the brain systems that support semantic processing are poorly understood compared to those of perceptual processing. However, as several of the functional neuroimaging studies have found, lateral frontal cortex is consistently involved in semantic language tasks (Demb et al., 1995; Gabrieli et al., 1996; Blaxton et al., 1996). Lateral frontal cortex, which may involve BA 46, 47, 9, and 8, was clearly involved in semantic decision tasks (Demb et al., 1995; Gabrieli et al., 1996) and

semantic word generation (e.g., Blaxton et al., 1996; Crosson et al., 1998; Warburton et al., 1996; Petersen et al., 1988). Interestingly, when patients with lateral frontal lobe lesions perform conceptual priming tasks, they perform normally (Mimura, Goodglass, & Milberg, 1996; Gershberg, 1997). Swick (1998) conducted a repetition priming study in which participants with frontal lobe lesions performed a lexical decision task that required them to decide if words were real words or not. Some words were repeated during the study, inducing faster reaction times (the priming effect). While this task does not have a clear conceptual priming approach to it, the interesting find was that the frontal lesion patients demonstrated normal behavioral performance while at the same time their event-related potentials (ERP's) were abnormal. ERP techniques are sensitive to subtle changes in electrical activity on the scalp and thought to reflect underlying brain activity. Thus, it appears that priming was normal by behavioral standards but abnormal by psychophysiological measures. With regard to functional neuroimaging, it could be that priming tasks are sufficient to produce changes in lateral frontal activity but that lateral frontal cortex is not the sole region of the brain that supports conceptual priming. This would explain the lack of convergence between lines of research in functional neuroimaging and research in patients with lateral frontal lesions.

For the purposes of this study, we will assume that lateral frontal cortex is involved in semantic language processing and that this region will be limited to the middle and inferior frontal gyrus (BAs 46, 47, 9, and/or 8). No more specific hypotheses will be entertained at the present time. The important distinction discussed below is between conceptual priming and motivation/initiation.

Medial frontal cortex

While there is some evidence to support the role of lateral frontal cortex in conceptual priming, evidence for the role of medial frontal cortex is scant. Why do other functional imaging studies of conceptual priming not result in decreased activation in medial frontal cortex, which seems to be so reliably involved in complex semantic processing and response selection (e.g., Crosson et al., 1999; Warburton et al., 1996; Petersen et al., 1988)? So far, no study has required subjects to generate the primed words during the study phase of the experiment. Instead, Blaxton and colleagues (1996) had participants think about how word pairs were related (though methodological problems limited interpretation), while Demb et al. (1995) and Gabrieli et al. (1996) asked subjects to monitor words for concrete or abstract qualities. Methodologically sound studies (Demb et al, 1995, & Gabrieli et al., 1996), found decreases in activation in left lateral frontal cortex due to priming, while no decreases in medial frontal activation were observed.

The data from Buckner et al. (1995) show that medial frontal activation occurred in the stem completion priming and the control tasks alone, but no difference in medial frontal activation occurred when the stem completion priming and control tasks were compared to each other. Why was medial frontal cortex not affected by this perceptual priming task? The stem completion task obviously recruited medial frontal cortex as seen in the control stem completion task, but the tasks did not differ in medial frontal activation as they did in cortex used for visual processing. As will be reviewed below, medial frontal cortex, including portions of SMA and anterior cingulate cortex, appears to be necessary for the generation of words. The priming test task used by Buckner and colleagues (1995) was a task of word generation and did not reduce medial frontal

activation, suggesting that some aspect of word generation was not affected by the priming. Lack of medial frontal priming effects might be due to the fact that the cognitive processes mediated by medial frontal cortex, namely the initiation of language output, did not overlap between study and test. Therefore, medial frontal areas related to language output did not become more efficient when the word was produced during the priming task since no transfer of initiation and word production processes occurred. As a result, medial frontal cortex showed no decrease in activation during priming.

Why have medial frontal cortical activation changes have not been observed in priming tasks that involve word generation (Demb et al., 1995; Gabrieli et al., 1996)? Stem completion, fragment completion, and generation of a semantic associate surely require initiation and response selection that reliably recruits medial frontal participation (e.g., Crosson et al., 1999; Warburton et al., 1996; Petersen et al., 1988; Buckner et al., 1995; Raichle et al., 1994). Again, it may be that the act of generating the word during study is necessary to show reduced activation in systems involved in initiation during test. Since Demb and Gabrieli required subjects to semantically process but not initiate the production of the primed words during the study phase, the initiation system (including medial frontal cortex) had no opportunity to become more efficient, while semantic systems did become more efficient.

Language output depends on the motivation/initiation system. The most dramatic evidence that such a system exists comes from patients who lack spontaneous language, including patients with supplementary motor area aphasia (a subtype of transcortical motor aphasia; Rothi, 1990; Benson, 1993), and akinetic mutism (Damasio & Anderson, 1993). Patients with supplementary motor area aphasia are typically in the acute phase of

brain injury or recovering from a more serious akinetic mutism (lack of spontaneous language in addition to lack of spontaneous movement), and they speak little, if any, on their own. When they are prompted, however, they can repeat words. Intact repetition is important in understanding that they can decode linguistic input at the lexical level and find a match in the phonological output lexicon, and they can hear and produce words. As the term "supplementary motor area aphasia" implies, these patients (and those with akinetic mutism) usually suffer strokes to the medial frontal cortex, including, but not limited to, the left supplementary motor area (medial BA 6), and left anterior cingulate cortex (BA 24) and the transitional cortex between them (paracingulate cortex of BA 32). Akinetic mutism typically arises from larger lesions in medial frontal cortex and results in a total lack of any activity, including language. Given the profound lack of spontaneous language that results from medial frontal lesions, most researchers ascribe motivation and initiation of language as key functions of these medial frontal areas (Goldberg, 1985; Benson, 1993; Damasio & Anderson, 1993; Rothi, 1990).

Functional neuroimaging studies of medial frontal cortex during self-guided word generation also support the role of medial frontal cortex in speech and language. Some studies use generation of verbs to given nouns (Peterson et al, 1988; Warburton et al., 1996; Raichle et al., 1994), while others use generation of words from a given category or starting with a given letter (Crosson et al., 1998; Phelps et al., 1997; Friston et al., 1991; Warburton et al., 1996). In all of these studies, there has been robust activation in medial frontal cortex. Most of these studies used group analysis, and they localized medial frontal activity to the anterior cingulate cortex, BA 32, and/or SMA. However, Crosson et al. (1999) noted that in most of their subjects, medial frontal activity was especially

prominent at the border between pre-SMA (the portion of area 6 anterior to SMA) and the paracingulate cortex (a portion of area 32) when data were analyzed on a subject-by-subject basis. Most authors attribute medial frontal activity to some aspect of the output or response side of processing, whether it is attention and selection from competing responses (Phelps et al., 1997; Petersen et al., 1988) or formulation or initiation of a strategy (Warburton et al., 1996; Crosson et al., 1998). If it could be shown that priming causes a reduction in activation in medial frontal cortex, then it is highly likely that priming has impacted the formulation or initiation of a response.

CHAPTER 3
PRACTICE: DEFINITION AND REVIEW

The emphasis in this dissertation thus far has been on changes in brain activation related to priming. Recall that priming is a form of implicit memory, or memory that does not require conscious recollection of the learning episode. Another type of implicit memory is skill learning (Squire, 1992). Priming and skill learning have three things in common: Both can be performed in the absence of conscious recall, as seen in patients with amnesia (e.g., Corkin, 1968; Butters, Heindel, & Salmon, 1990); both are characterized by an improvement or facilitation in behavioral performance (i.e., greater efficiency; Nissen, 1992); and both result in changes in patterns of brain activation (Petersen et al., 1998). While it is commonly believed that skill learning and priming are independent phenomena (e.g., Schwartz & Hashtroudi, 1991), it may be that skill learning and priming share some common anatomic substrates. For example, if persons practice word generation, will their performance become faster and more efficient, and will that increased efficiency be reflected in increased biological efficiency? If priming shows subtle changes in brain blood flow after a single encounter with a particular item, how soon do practice-related changes in brain blood flow appear? Raichle et al. (1994, reviewed below) have addressed the former question by having participants perform a language task repeatedly and comparing patterns of brain activation before and after the task became automatic. Experiment 2 of this dissertation will address the latter question.

Raichle and colleagues (1994) observed profound changes in brain activity when a verbal task was rehearsed numerous times. While this study is not specifically a

priming study, it bears many elements of priming, including repeated exposure to stimuli and no explicit recall instructions, as just noted. Participants underwent PET scans while generating verbs that appropriately matched given nouns (e.g., cake - *eat*). Scans taken during the first performance of the task were compared to scans taken during the tenth practice trial. Given the extensive rehearsal and the remarkable consistency of responding (85% of responses were repeated after 4 practice trials), it is likely that the processing involved, at least in part, conscious recall as opposed to priming. Initial performance of the verb generation task produced robust activation in left prefrontal cortex, anterior cingulate cortex, and right cerebellar cortex, just as other generation tasks did. However, the practice caused a significant reduction in activity for these three areas. Practice also caused an *increase* in activation in perisylvian cortex and inferior frontal cortex. When the practiced generation task was compared to a more automatic language task (repetition), no differences were found. In essence, a task that was initially effortful became indistinguishable in patterns of brain activity from a simpler task when the task was practiced. The authors concluded that brain areas used during the initial word generation task are related to complex knowledge and response selection, while brain areas active during the learned task were related to automatic, proceduralized linguistic processing.

The study by Raichle and colleagues (1994) has implications for priming, even though priming is not its primary focus. First, the fact that activation changes were seen with repeated performance is similar to studies of priming. In word generation priming, just as in Raichle's practiced generation, the participant repeatedly uses words, with a resulting increase in likelihood that the studied word will be chosen as a response.

Similar to other functional imaging studies of priming, Raichle et al. (1994) noted a decrease in activation in brain areas used for such processing. However, Raichle's task is not necessarily a conceptual task by the time it is overlearned. In fact, as Raichle has concluded, the task becomes more automatic and less effortful. As the task becomes more automatic, subjects are not putting as much effort into the task and not engaging in the complex processing that appears to be important for dorsolateral and medial frontal activation. If dorsolateral and medial frontal cortex are involved in complex semantic processing and response selection, then conceptual priming should lead to a reduction in activation in these areas, just as Raichle et al. (1994) observed with their overlearned task. If conceptual priming does not involve these processes, then practice alone will result in changes in medial frontal activation. To compare the different affects of practice and priming, a practice task has been included in this study. The method used here is different from that used by Raichle et al. in that only three practice trials are administered to each participant instead of ten, and scans were obtained in all three trials. The purpose of reducing the number of practice trials was to determine whether a smaller amount of practice was sufficient to detect changes in patterns of brain activation.

CHAPTER 4
HYPOTHESES

This proposal will test the hypothesis that semantic processing that involves both semantic and motivation/initiation systems will affect medial frontal and dorsolateral frontal cortex. Dorsolateral prefrontal cortex is involved in processing the meaning of words, and it has been shown that when the second instance of the word is encountered and/or produced, dorsolateral prefrontal cortex shows a decrement in the degree of functional activation. Medial frontal cortex is involved in the initiation and production of linguistic responses. Little evidence currently exists that medial frontal cortex will show a decrease in the magnitude of activation, but the hypothesis that implicit memory processes can affect medial frontal activation will be tested as well. Priming effects on medial frontal cortex will be compared to practice affects on medial frontal cortex.

Functional magnetic resonance imaging (FMRI) is an effective tool for observing the effects of priming on the brain (Demb et al., 1995; Buckner et al., 1995). FMRI is sensitive to changes in blood oxygen concentration, which in turn are closely related to neural energy consumption and therefore neural activity (Nadeau & Crosson, 1995). Increased blood flow occurring in active brain areas overcompensates for the oxygen that is used by active neurons. When two functional images are compared and a difference occurs, a decrease in signal detected by FMRI indicates lower levels of oxygenated blood in one image (or set of images), and presumably less neural activity. If priming reflects the progression of a neural system to a more efficient state, then the effects of priming on neural systems can be detected as a decrease in FMRI signal during the primed task

versus the unprimed task. The specific hypotheses to be tested in the following experiments are:

1. Category exemplar generation (CEG) priming can be observed in normal human participants. Category exemplar generation will result in the production of more exemplars than were previously produced in a word-cued association study task.

2. FMRI will be sensitive to increased oxygenated blood flow to medial frontal cortex (pre-SMA and paracingulate cortex, i.e. Brodmann's areas 6 and 32) and lateral frontal cortex (BAs 46, 47, 9, and/or 8) during category exemplar generation for both primed and unprimed categories.

3. CEG priming will result in a decrease in functional activation observable through FMRI. Activation decreases will include:

   (a) Lower average signal and/or smaller volumes of activation in lateral frontal activation (BAs 46, 47, 9, and/or 8) related to more efficient semantic processing related to priming;

   (b) Lower average signal and/or smaller volumes of activation in medial frontal cortex (pre-SMA and paracingulate cortex) related to increase efficiency selecting and producing primed category exemplars.

4. Repeated category exemplar generation for unprimed categories will result in a lower average signal and/or smaller volumes of activation in medial frontal activation (pre-SMA and paracingulate cortex) due to facilitation of response selection and production. In addition, it is hypothesized that an increase in the same indices of activation in inferior lateral frontal activation (BAs 44, 45, 47 and

perisylvian cortex) will occur as the task become more automatic and relies on areas of inferior lateral left frontal cortex that are thought to support more automatic language processing. It is expected that both of these changes in activation will be detectable after a short period of practice (three trials).

It should be noted that BA 47 is contained in orbitofrontal cortex, which is a region that was not sampled using the current FMRI technique due to signal loss related to artifact caused by the air-tissue interface in the nasal sinuses located directly beneath orbitofrontal cortex. While the previous hypotheses were proposed based on prior literature, no analyses of BA 47 was possible due to the inability to image orbitofrontal cortex. Therefore, there will be no references to BA 47 in the subsequent sections.

CHAPTER 5
EXPERIMENT 1

Experiment 1 was conducted to ascertain that procedures and stimuli developed for CEG priming would produce effects for at least some subjects. It was a pilot study for Experiment 2 in which the same methods were used to examine the effects of priming on medial and lateral frontal regions using FMRI. The basic experimental design consisted of 3 tasks. (a) The Association task required participants to generate semantic associates to given cues. A total of 90 association trials were administered, including 45 trials for which the correct response was an exemplar from the one of the nine primed categories. The other 45 association trials were distractor trials. Cabeza (1994) presented data to suggest that a category classification task (to what categories does it belong?) would result in a larger priming effect, but this task was not used to avoid potential contamination of explicit recall in the priming task due to a more obvious connection brought about by the repeated reference to categories between study and test phases. (b) The Generation task required participants to produce as many category exemplars as they could from each of the 18 categories. Nine of the categories were primed in that participants had produced five exemplars from each primed category during the Association task. (c) The final task was the Practice task, which required participants to produce as many category exemplars as possible from unprimed categories repeated over two additional trials.

Methods

Participants

Eleven participants (10 female, 1 male,) were recruited from the staff, student, and community population of the University of Florida and Gainesville, Florida. All participants were right-handed (Edinburgh Handedness Inventory; Oldfield, 1971; mean = 84.9, SD = 23.8), native English speakers, and between the ages of 18 and 23 (mean = 20.7, SD = 1.3). Participants were excluded if they had neurological conditions that disrupt cognitive functioning, such as a history of head injury (with loss of consciousness greater than 30 minutes or with significant cognitive impact), neurodegenerative conditions, stroke, or other conditions that compromise the central nervous system. Potential participants were also excluded if they had a history of a formally diagnosed learning disability, current diagnosis of major depression, current or past diagnosis or treatment for psychotic or bipolar disorders, or history of substance abuse. Participants were screened by telephone interview before being invited to participate, and they were administered a written screening questionnaire with the above criteria upon arrival.

Materials

Eighteen categories were chosen from Battig & Montague (1969) and separated into two lists (A and B). Each category had at least 10 members. Five exemplars were chosen from each category which met the following criteria: Each word had a category typicality rating of at least 8, each had a one- or two-word semantic associate that could serve as a semantic cue, and each was a noun. List A and B category exemplars were matched in mean typicality ratings (list A mean = 17.2, SD = 7.9; list B mean = 16.4, SD

= 8.2; $t = 0.42$, $p > .30$). Words that were less typical of the category were chosen to increase the likelihood that a target word was produced due to priming effects rather than due to the base rate probability of being produced because it is a typical member of the category (Battig & Montague, 1969). Semantic associates were chosen such that no semantic associate was also a member of list A or B categories. In addition, 45 distractor nouns and corresponding semantic associates were chosen for the study task to reduce the likelihood that participants would notice that items from particular categories were recurring. In sum, the stimulus materials consisted of 18 category names, 5 exemplars from each category, a semantic associate for each exemplar, 45 distractor words and 45 corresponding semantic associates.

Stimuli (90 category exemplars, and 90 semantic associates, 45 distractors, and 18 category names,) were recorded using commercially available digital recording software (Sound Editor – IRIS Audio Recorder/Editor for Irix 6.2, Silicon Graphics Inc.). Recorded words were transferred to a personal computer, on which custom software (Gökçay, 1996) was used to organize the stimulus presentation. The actual stimuli were recorded onto audiocassette from the computer, and participants were tested using these cassettes.

Design

Each participant was administered the Association task, the Generation task, and the Practice task in that order. Participants responded out loud on all tasks in Experiment 1 so that all aspects of their performance could be measured and used to estimate performance of participants in Experiment 2. The Association task was administered first to engage the participants in processing the chosen category exemplars. The Generation

task was then administered to determine whether prior processing during the Association task resulted in production of primed exemplars. Finally, participants engaged in two more sets of generation in a task called the Practice task because they repeated a task that was done earlier and were encouraged to say the words that came fastest and easiest. During the Practice task, participants were presented the last six unprimed categories that they encountered during the Generation task, and they were asked to produce category exemplars twice more to those categories. Participants were expected to become more efficient at producing words from the repeated categories.

Experimental Tasks

In the study phase, participants completed the Association task. On this task, participants heard a one- or two-word semantic cue followed by the first 1-3 phonemes of the target response. The semantic cue was chosen to be highly associated with the target item, thus increasing the probability that the participant would select the desired response. High strength associates were determined through pilot data collection as well as from previously collected normative data (Nelson, McEvoy, & Schreiber, 1994). The task of the participants was to produce the response that was related to the semantic cue and that began with the given phonemes. The phonemic cue was provided to ensure that the target response was the desired response. Each phonemic cue was required to be common to at least three English words. A total of 90 association trials were completed, including 45 trials for which the target responses came from one of the nine primed categories, and 45 distractor trials. Trials were presented at a rate of one every 8 seconds. For example, a participant heard the semantic cue "log.../cab/", and they were to say "cabin." Participants correctly completed 40.3 of 45 association trials on average (89.5%

correct). The Association task was continuous and lasted for 12 minutes. Any target item that was not produced correctly during the Association task was excluded from the analysis as a possible target.

The Generation task was completed in three separate segments as would occur during the FMRI study in Experiment 2. Each segment consisted of the presentation of 6 categories interleaved with 6 rest periods plus an additional rest period at the end. Thus, a total of 18 categories were presented in three sets of six. Each category generation period began with the category name followed by the word "begin" (e.g., "Birds. Begin."). Participants produced as many words as they could, until they heard the word "end." Each category generation period lasted for 26 seconds. After a rest period of 17.4 seconds, the next category was presented. Categories were presented in three sets of six, since this structure would be followed in the scanner.

The Practice task was always conducted last, since it utilized some of the categories from the Generation task. The last six unprimed categories were grouped together and administered to each participant. The structure was identical to that of the Generation task (17.4 sec of rest alternating with 26 seconds of generation). Participants were instructed only to produce the items that came fastest and easiest for each category. Participants generated exemplars to these six categories twice.

Procedure

After informed consent was obtained, participants were seated in a testing room where instructions were read in a standard fashion. They were told that these tasks were to be used later in a brain imaging study. For the Association task, participants were instructed to listen for cues and word parts and to respond with an item that is related to

the cue and that begins with the given phonemes. They were given 3-5 practice trials. Once the subject demonstrated understanding of the task, the taped stimuli were started. The experimenter remained in the room, recording each response.

After the 90 association trials were completed, the participant was instructed on the Generation task. They were told that the next task was a category word production task. They were asked to say names of items from categories that they would hear, and they were encouraged to produce at least 8 items from each category in the time allotted before they heard the word "end." Participants were asked to keep their minds as empty as possible between categories during the rest period. No mention was made that the Association task and the Generation task were related. Each participant was given 2-3 practice trials. Once the participant demonstrated understanding, a tape recorder was started to record each response. The examiner then started the stimulus tape and left the room. The examiner left the room to remove any effects on task performance by the examiner being present, with the purpose being to replicate the isolation that would occur in Experiment 2 when participants would be responding to themselves in the scanner. After each set of six categories was completed, the examiner would return and ask the participant if he or she heard all of the categories, just as would occur in Experiment 2. Later, participants' responses were transcribed from the audio tape recordings.

After all 18 categories of the Generation task were administered, the examiner returned and performed a recognition memory test. Recognition memory was tested to validate recognition as an accurate method by which participants' responses on the Generation task could be monitored. A recognition probe was necessary because participants would not be allowed to speak out loud during the Generation task while in

the scanner during Experiment 2, and a recognition probe would give some indication about their performance. Participants were given a list of category names and exemplars, and they were asked to place a check next to each category exemplar they produced during the Generation task. Their responses were compared to their actual responses that were audiotape recorded to validate this method of data collection. After the recognition probe, a brief questionnaire about their strategy and use of conscious recall was administered. One participant who used conscious recall was excluded.

The Practice task was then introduced. Participants were told that they would produce more words from categories, and that it was important that they say the items that come fastest and easiest. The last six unprimed categories were administered. The examiner returned to monitor whether they were hearing the stimuli, and the last six unprimed categories were administered again, in the same order. After the Practice task was concluded, all participants were debriefed regarding the true purpose of the experiment in the interest of providing complete information and asked not to share the true purpose with anyone they knew would be participating at a later date.

<u>Analyses</u>

Primed and unprimed category exemplar generation were compared using a within-subjects t-test on proportion of targets produced (referred to as "proportion correct") as the dependent variable and primed/unprimed as the within-subjects independent variable. Targets for primed and unprimed categories consisted of 5 preselected exemplars from each category that were matched on typicality between the primed and unprimed categories, as described above. Proportion of targets produced was defined as the number of targets produced during the Generation task divided by the

number of available targets. Recall that if a participant did not produce the target correctly during the Association task, it was excluded from further analysis as a potential target. Recognition was analyzed by comparing agreement rates between recognition memory to actual performance based on audio taped generation performance. Practice effects were analyzed with an ANOVA with practice trial as a within subjects factor with three levels: first, second, and third encounter with the categories. The three encounters include the first time participants produced exemplars from the unprimed categories during the Generation task and the subsequent two times the participants produced exemplars during the Practice task.

Results

Priming Results

Table 1 contains results from the priming portion of Experiment 1. Recall that proportion correct is the ratio of target items produced divided by the total number of available targets, and that targets for unprimed categories consisted of preselected words matched on category typicality ratings to those from the primed categories. Participants produced significantly more target words in the primed categories than in the unprimed categories, $t = 2.57$, one-tailed $p < .02$. The magnitude of priming was .051 (or 5.1%) more target words produced for primed categories relative to unprimed categories. Table 1 also contains the average number of words produced for primed and unprimed categories. There was no difference in average production rates between primed and unprimed categories ($t = 0.65$, two-tailed $p > .5$), indicating that priming is not simply due to different production rates between the two sets of categories.

Table 1. Proportion of Correct Words that Were Primed and Average Number of Words Produced for Primed and Unprimed CEG

	Primed	Unprimed	Magnitude of Priming [a]	Primed Produced [b]	Unprimed Produced [b]
Mean	.237	.186	.051	9.7	9.4
SD	.08	.06	.066	2.6	1.6

[a] Difference between primed and unprimed proportion correct
[b] Average number of words produced for each category

Table 2 contains results from the recognition probe analysis. Participants' self-report on a recognition memory test was compared to actual performance for exemplars produced during CEG priming. Participants performed with greater than 90% accuracy on the recognition probe. There was no difference in accuracy between primed and unprimed recognition performance, $t = 1.48$, two-tailed $p > .1$. The average error rate per subject on the recognition probe was 0.55 omissions of targets they had actually produced and 1.0 false positive identification for targets they said they produced but actually did not. These error rates were not statistically significant between primed and unprimed categories (two-tailed p's > .5).

Table 2. Percent Correct on Recognition Probe Compared to Actual Performance

	Recognition Primed	Recognition Unprimed
Mean	.92	.93
SD	.05	.06

Practice Results

Table 3 contains the average number of words produced from the three trials of practice. These data are based on performance in the first 20.88 seconds of word production to make the data comparable to that in Experiment 2, since participants in

Experiment 2 had only 20.88 seconds to generate words from each category instead of the 26 seconds in this experiment. Any words produced beyond 20.88 seconds were not included in the following analysis. Analysis of Variance indicated that the average number of words produced was different between practice trials, $F = 6.7$, $p < .01$. Post hoc t-tests indicated that participants produced more words in Trial 3 than in Trial 2 ($t = -6.08$, two-tailed $p < .001$), and they produced more words in Trial 2 than in Trial 1 ($t = -4.9$, two-tailed $p < .001$).

Table 3. Average Number of Words Produced for Each Category across the Three Practice Trials of Category Exemplar Generation

	Trial 1	Trial 2	Trial 3
Mean	8.5	9.7	11.1
SD	1.5	1.6	1.8

Figure 4 depicts the number of common words shared among the successive practice trials. As can be seen, the number of words shared by successive trials increased as practice progressed. The number of shared words among all three trials is depicted in the last column. When the number of shared words is compared to the average number of words produced, between 65% and 80% of all words produced for each category were produced in one or both of the previous practice trials.

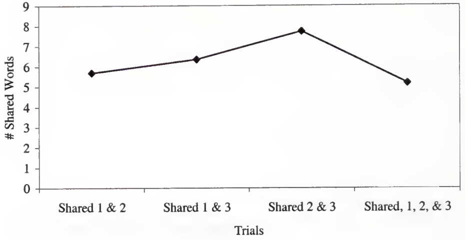


Figure 4. Average number of shared exemplars between practice trials, n = 11.

Discussion

Priming

The results of Experiment 1 support the conclusion that this methodology can reliably produce CEG priming. The magnitude of CEG priming was approximately 5% for primed categories compared to unprimed categories. This is a smaller magnitude than seen in other studies, which typically find 8-20% CEG priming magnitude (e.g., Keane et al., 1997; Gabrieli et al., 1995; Light & Anderson, 1989; Hamann, 1990). This difference in priming between the present study and previous studies can be explained by differences in methodology. Most prior studies did not use any distractor items during the study phase. The introduction of distractors during the study phase may have caused interference and therefore reduced the magnitude of priming. In addition, most studies did not attempt to prime 9 categories at once as in the present study. Instead, they would attempt to prime 3-6 categories at any one time. The one study that primed a large

number of categories (12 categories, Keane et al., 1997) saw the lowest magnitude of CEG priming (8%). Taken together, these two methodological differences may have served to dilute the priming effect slightly. While other studies may have utilized more powerful methodologies, the methods utilized here are considered important for two reasons. First, a large number of categories is necessary to obtain adequate statistical power due to the analysis methods (see Experiment 2 Data Analysis). Second, a large number of distractors was considered necessary to prevent participants from perceiving the presence of semantic categories. If categories were detected during the Association task, it would be more likely that participants would be able to identify them during the Generation task and subsequently to use conscious recall. As Schacter and Buckner (1998a) have discussed, conscious recall can result in specific patterns of activation in functional neuroimaging studies (e.g., right frontal activation) that could confound the results if they occurred in this study.

Practice

When participants repeatedly produced words to the same semantic categories, behavioral facilitation occurs in the forms of production of more words and production of similar words over successive practice trials. This demonstrates that changes in behavior can be measured over the three practice trials on a category generation task. Raichle et al. (1994) observed changes in patterns of brain activation over the course of 10 practice trials (generating a verb that is associated with a given noun). This study will attempt to observe changes in brain activation after only three practice trials to determine when in the course of practice changes in brain systems can be detected.

CHAPTER 6
EXPERIMENT 2

As we saw in Experiment 1, priming of category exemplar generation can be achieved with a methodology that is compatible with the scanning environment. In Experiment 2, we apply the same method to participants undergoing FMRI. The tasks were identical to those in Experiment 1 except for the changes noted below. Images obtained while subjects produced words to primed categories were compared to images obtained while subjects produced words to unprimed categories to test the hypothesis that activation decreases in medial and lateral frontal cortex will be observed during CEG priming. The priming analysis included only participants whose magnitude of priming exceeded that observed in Experiment 1. In addition, images obtained while subjects repeated the generation task three times for the same set of categories were compared to test the hypothesis that a small amount of practice can result in a decrease in medial frontal cortex and an increase in lateral inferior frontal cortex activation. All participants were included in the practice comparisons.

Methods

Participants

Criteria for participants were the same as in Experiment 1 with the additional criteria that participants with metal in their body or who were claustrophobic were excluded from Experiment 2. Potential participants were excluded if they had neurological conditions that disrupt cognitive functioning, such as a head injury (with

loss of consciousness greater than 30 minutes or with significant cognitive impact), neurodegenerative conditions, stroke, or other conditions that compromise the central nervous system. They were also excluded if they had a history of a formally diagnosed learning disability, current diagnosis of major depression, current or past diagnosis or treatment for psychotic or bipolar disorders, or history of substance abuse. Each participant was initially screened over the telephone after expressing interest in the study. Recruitment occurred through undergraduate courses and through posted advertisements throughout the campus and hospital. Participants who met inclusion criteria were scheduled and reminded that all metal would have to be removed from the face and head for the scan.

Twenty-eight participants (13 male, 15 female) were recruited from the staff, student, and community population of the University of Florida and Gainesville, Florida. All participants were right-handed (Edinburgh Handedness Inventory; Oldfield, 1971; mean = 84.7, SD = 13.8) and native English speakers. The average age was 25.5 years (SD = 7.5), and the average education level was 16.4 years (SD = 2.5). Ten additional participants were excluded for various reasons, including four participants who demonstrated visible head movement when functional time series were viewed in a cine fashion, five participants whose data were corrupted (e.g., slice prescription errors, scanner malfunction, or stimulus presentation errors) and one participant who was claustrophobic. All participants completed both the priming phase and the practice phase of this experiment. However, only those participants whose magnitude of priming exceeded the average magnitude of priming from Experiment 1 plus ½ of a standard deviation were included in the FMRI priming analysis. The pilot data collected in

Experiment 1 yielded a magnitude of priming of 5.07% (SD = 6.6%), which represents an average 5.07% increase in production of target words for primed categories compared to unprimed categories. Thus, to be included in the FMRI priming analysis, a participant must demonstrate a magnitude of priming that equals or exceeds 5.07% plus (6.6% ÷ 2), or 8.3%.

Materials

The stimuli for Experiment 2 were identical to those used in Experiment 1, except that stimuli were presented over a portable computer instead of audiotapes. Stimuli were presented from an IBM 380ED notebook computer using custom written software (Gökçay, 1996). Output from the computer was amplified using a Kenwood KR-A-4070 amplifier and biased toward the high end of the frequency spectrum using a Realistic 31-2005 Ten Band Stereo Frequency Equalizer to compensate for high frequency loss through the air conduction apparatus. A JBL 2446J 16-ohm speaker was attached to an insulated air conduction transducer consisting of flexible nonmetallic tubing surrounded by foam insulation to dampen ambient noise. Foam insert earphones were positioned in the external auditory meatus as the final link in the air conduction transducer. These foam inserts attenuate scanner noise by ~20 dB sound pressure level (Binder et al., 1995). Before beginning experiments, words were played above threshold while the scanner was operating, and sound levels were reduced until target words in a list could no longer be distinguished. Then stimuli were delivered at 30-35 dB above this threshold. A second insulated air conduction tube similar in design to the air conduction transducer described above was placed above the participant's face to record responses for the Association task only. The tube carried the participant's voice outside the scanner where responses

were recorded via a small microphone inserted into the end of the tube and recorded onto a Sony portable cassette recorder.

Procedure

Upon participants' arrival at the scanner, informed consent was obtained according to guidelines put forth by the University of Florida Health Science Center Institutional Review Board. Participants were screened again to ensure they met all inclusion criteria and safety guidelines (e.g., free of metal in the body, not claustrophobic).

Once safety requirements were met, participants were instructed and trained on the tasks prior to entering the scanner. Instructions for the Association task and the Generation task were the same as in Experiment 1. Participants were first read the instructions for the Association task and given 3-5 practice trials. Once each participant demonstrated an understanding of the Association task, instructions for the Generation task were administered. Two or three practice generation categories were administered. Since the instructions for the practice were essentially the same as the Generation task, participants were given Practice task instructions immediately prior to the practice runs in the scanner.

Participants were seated on the scanner bed and the earphone inserts were placed snugly in their ears. Then, the participant was laid down on the scanner bed and his or her head was placed inside the head coil and stabilized using foam pads inserted in the space between the head coil and the temples and forehead, with an additional pad beneath the neck. After the sound threshold and volume level were established, slices were prescribed and the MR angiogram collected. The scanner was then prepared to run

during the Association task, though no FMRI data was collected during the Association task. The scanner noise was utilized to present the appearance that the Association task was another FMRI task and unrelated to the Generation task. Instructions were repeated immediately prior to the 12-minute Association task.

The Generation task was started immediately after the end of the association task by repeating the instructions for the task. FMRI data were collected in a series of 3 runs. Each run consisted of 6.4 cycles (one additional rest period at the end); each cycle consisted 20.88 sec periods of rest alternating with 20.88 sec periods of category exemplar generation. During the rest periods, participants were instructed to keep their eyes open and focused on a predetermined fixed point. During the category exemplar generation task, participants were instructed to say covertly, to themselves, as many category items as they could in the time they were given, trying to produce at least 8 items for each category. Each Generation period lasted 20.88 seconds and consisted of the presentation of the category name followed by the word "Begin." Participants then produced as many exemplars to themselves until they heard the word "End," which signaled the end of that particular category generation period. The Generation duration is shorter than that used in Experiment 1 due to constraints on the amount of FMRI data that could be collected over the entire run.

A recognition memory task was administered after all 18 categories (nine primed, nine unprimed) were administered. The recognition test consisted of the examiner stating the category names and five target exemplars from each category. Participants, who remained in the idle scanner, said "yes" if they produced that item during the Generation task. Experiment 1 indicated that recognition accuracy was greater than 90%. The

number of primed target items produced was compared to the number of unprimed target items to determine the magnitude of priming for each participant.

Following the recognition memory test, the Practice task was administered. The Practice task consisted of two additional runs that were identical in structure to the Generation task runs, except that the categories consisted of the last six unprimed categories from the Generation task. Participants were instructed to say the items that came fastest and easiest, just as in the Raichle et al. (1994) study. As noted above for the priming tasks, the duration of each category generation period was shorter than that used in the pilot study due to constraints on the amount of FMRI data that could be collected. Following the practice tasks, high-resolution 3-D anatomic scans were obtained. Participants were then removed from the scanner and debriefed as to the true purpose of the study.

FMRI Data Collection

FMRI was conducted on a 1.5 Tesla MRI scanner (Signa, General Electric Medical Systems, Milwaukee) equipped with a dome-shaped quadrature radiofrequency head coil constructed at the University of Florida (Peterson & Fitzsimmons, 1994). T1-weighted axial scout scans were acquired to determine location of sagittal functional images. To ensure optimal coverage of the medial frontal cortical surface, head alignment in the coil was adjusted, if necessary, such that the interhemispheric fissure was within 1° of vertical. The medial sagittal slices for the functional scans were placed such that the point of adjacency between the two medial slices was located in the interhemispheric fissure, reducing the likelihood of volume averaging between left and right hemispheres on the 5.4 to 6.5 mm slices of the functional scans. Twenty-two slices

covering the entire brain were acquired. Before functional images were acquired during task presentation, a time-of-flight MR angiogram (TE = 7.7 ms, TR = 40 ms, FA = 60°, FOV = 18 cm, matrix = 256 x 256) was acquired with exactly the same 22 slices used for functional images. In this way functional images could be overlaid onto MR angiogram slices to ascertain the existence of large vessel effects. For functional scans, a series of 77 images was acquired for each of the 22 sagittal slices using a gradient echo spiral scan technique (Noll et al., 1995) with TE = 40 ms, TR = 1740, FA = 60°, FOV = 18 cm, and two spirals. The 77 images allowed for 6 images to be collected during each task epoch, making each task epoch (generation or rest) 20.88 sec in duration. An additional series of 5 images were collected at the end for a final period of baseline rest. Subsequent to functional imaging runs, structural images were acquired for 124 x 1.3 mm thick sagittal slices using a 3-D spoiled GRASS volume acquisition (TE = 7.0 ms, TR = 27 ms, FA = 45°, FOV = 24 cm, NEX = 1, and matrix = 256 x 192).

<u>Data Analysis</u>

<u>Priming.</u> Data were analyzed using AFNI software (Cox, 1996), using the techniques outlined by Binder et al (1997). Raw functional time series were first corrected for motion to eliminate artifact caused by movement. A 3-D image registration technique was applied that utilizes an iterative procedure that minimizes variance between two images (Woods et al., 1992). All images were registered to the last image of the last run, since it was closest in time to acquisition of the 3-dimensional anatomic images and ensured the most accurate placement of the functional images onto the anatomic images. After registration, if more than 5 images per run showed uncorrected movement when viewed in a cine fashion, the participant was excluded. Four

participants were excluded on this basis. Estimated indices of displacement and rotation are listed in Table 4 for all 28 participants.

Table 4. Average Displacement (mm) and rotation (degrees) after 3-Dimensional Image Registration Across All Images and Slices.

Movement Dimension	Mean	SD
Inferior displacement	0.16 mm	0.13
Right displacement	0.10 mm	0.06
Posterior displacement	0.10 mm	0.04
Roll	0.0033°	0.06
Pitch	-0.12°	0.1
Yaw	-0.068°	0.07

The signal intensities associated with the conditions (rest, primed, and unprimed) were compared using t-tests on a voxel-by-voxel basis. Each epoch was designated as either primed, unprimed, (probe epochs) or rest (control epoch), depending on the activity in which the participant engaged at the time. Six images were obtained during each epoch. Within each probe epoch, the final four images were retained for within-participant t-test analysis. These four images were chosen ensure that the hemodynamic response had time to stabilize after it reached its peak within the half-cycle. These images were averaged into one image, containing the average signal across the final 13.9 seconds of the probe epoch. Next, images from control epochs surrounding the probe epoch (eight images were averaged, including four from each control epoch except the last control epoch from which only 3 images were available) were averaged and subtracted from the probe epoch image, creating a difference image between probe and control epochs. Using baselines that surround the probe epoch compensates for any drift in signal caused by slight changes in head position or changes in the scanner

environment. This difference image was compared to a hypothetical mean of zero using a paired samples t-test. The final product for each participant is a statistical map of t-values corresponding to the various degrees of difference between probe and control tasks. These differences were referred to as "activation" for the sake of simplicity. As noted above, nine category generation periods per condition (primed, unprimed) were utilized to ensure adequate degrees of freedom, since degrees of freedom is determined by the number of task states (e.g., 9 category generation periods will yield 8 degrees of freedom for a paired t-test). A minimum of 7 task states is required to meet the minimum 6 degrees of freedom necessary to yield an accurate estimation of the distribution of averaged t-values for the group analysis described below (Fisher & Cornish, 1960).

Primed and unprimed Generation trials were directly compared using a paired samples t-test. Areas were considered activated if the p-value was greater than 0.001, as was used in Binder et al., 1997. After all participants have been analyzed individually, they were combined in a group analysis. First, each participant's data was converted into standard atlas space (Talairach & Tournoux, 1988) using AFNI software (Cox, 1996). Fiducial points in high-resolution anatomical images on the anterior commissure, posterior commissure, midsagittal plane, and edges of the brain were used to interpolate images into standard atlas space. Then, to compensate for individual variation in anatomy, the stereotaxically converted activation images were smoothed to the average of all voxels within a 3-voxel radius. Smoothed t-test data was averaged across participants and thresholded to identify voxels containing meaningful change. The threshold was set using the Cornish-Fisher expansion method (Fisher & Cornish, 1960) to account for the fact that the distribution of t-scores is not a tabulated distribution. The degrees of

freedom were eight, based on nine primed (or nine unprimed) categories minus one. As described above, only participants whose magnitude of priming exceeded the 8.3% threshold were included in the priming analysis. Eleven out of 28 participants met inclusion criteria for the priming analysis.

Practice. The analysis of FMRI data collected during the Practice task was analyzed using a voxel-by-voxel, one-way, within-subjects Analysis of Variance (3dANOVA2). The factor of interest was practice, which contained three levels corresponding to the three times each participant generated exemplars to the same category. The ANOVA was conducted on the same difference images described above. Each practice FMRI run consisted of 6 probe epochs interleaved with 6.4 rest epochs. As with the priming analysis, the last 4 images of each epoch were averaged, and the average of the two rest epochs surrounding each probe epoch was subtracted from the probe epoch (in this case, the practice epoch). This subtraction created a difference image. Difference images were then averaged across probe epochs within each level of practice (i.e., all probe epochs within a practice run were averaged). There were three resulting sets of differences images corresponding to the three levels of practice. At this point, the within-subjects ANOVA was conducted on the difference images. The null hypothesis is that the difference between rest and active states was equal at each level of practice. A voxel was considered active below the threshold of $p < .001$. If there was a cluster larger than that assumed to be by chance (see below), it was interpreted based on post-hoc t-test comparisons of the means at each level of practice. As in the Priming analysis, t-tests were also conducted to test the hypothesis that the difference in signal between the probe and rest epochs was nonzero. For the Practice data, however, these individual statistical

parametric t-maps were only used in the post-hoc time series analysis that will be described below.

To determine the minimum volume of activation to be interpreted for both the priming and practice analyses, time series images were randomized and re-analyzed. No volume less that the largest occurring during the random time series analysis was interpreted. For the practice analysis, this minimum volume was determined to be 164 microliters for the ANOVA and 305 microliters for the post-hoc t-tests at $p < .001$. For the priming analysis, there were no volumes of activation in the random time series analysis at the $p < .001$ level. In fact, the random time series yielded volumes of activation (47 microliters) only at $p < .025$. To be conservative, no volume smaller than 47 microliters was interpreted for the priming analysis even though the significance level for interpretation of the actual time series was $p < .001$ and the p-value for the random series was .025.

To determine the anatomic location of activated regions, group statistical maps were subjected to a cluster analysis. Cluster analyses yielded the volumes of contiguous pixels that exceeded the threshold of $p < .001$. Cluster analyses also yielded the anatomical center and the extent (both in stereotaxic coordinates) of the volumes, though some clusters extended across several anatomic regions and could not be separated into individual centers. Functional localization of clusters was determined by comparison of cluster coordinates to those in a standard atlas (Talairach & Tournoux, 1988). Any cluster that occurred primarily in the space occupied by a large blood vessel as determined by overlaying activation maps onto MR angiograms, was not interpreted.

Individual Medial Frontal Activation Analysis. An exploratory post-hoc activation volume analysis on individual participants was conducted to assess whether the group analysis was insensitive to activation changes between task states. Activation volumes from individual participants were selected form left medial frontal cortex and compared between task states (primed vs. unprimed and practice levels 1 vs. 2 vs. 3). An activation volume was determined to be within left medial frontal cortex if it was above the corpus callosum and situated between the plane ascending from the genu of the corpus callosum and the plane ascending from the posterior commissure. These two planes were chosen because between them lies both SMA and pre-SMA (Picard & Strick, 1996). The volume must exceed the maximum cluster occurring by chance for that individual, which was derived from the random image analysis. Each voxel in the cluster must exceed $p < .001$ in significance for the primed or unprimed analysis and $p < .01$ for the practice analysis. Different significance levels for the priming and practice analyses were chosen because the practice analysis had fewer degrees of freedom. Since the degrees of freedom for the individual participant's t-test is the number of active task states minus one, a slightly lower threshold was chosen to increase sensitivity for the practice analysis since practice occurred with six periods of CEG as compared to the nine period of CEG in the priming task states. Clusters that primarily existed on top of veins or arteries based on comparison to individual MR angiograms were excluded, which accounted for less that 5 % of medial frontal clusters. Lateral frontal regions associated with semantic processing and priming are more varied in location in previous studies (e.g., Buckner et al., 1995; Gabrieli et al., 1996) than medial frontal regions associated with language production (e.g., Warburton et al., 1996; Crosson et al., 1999; Picard &

Strick, 1996). Due to the lack of specific anatomic boundaries from previous literature, lateral volumes of activation were not analyzed with this technique.

Results

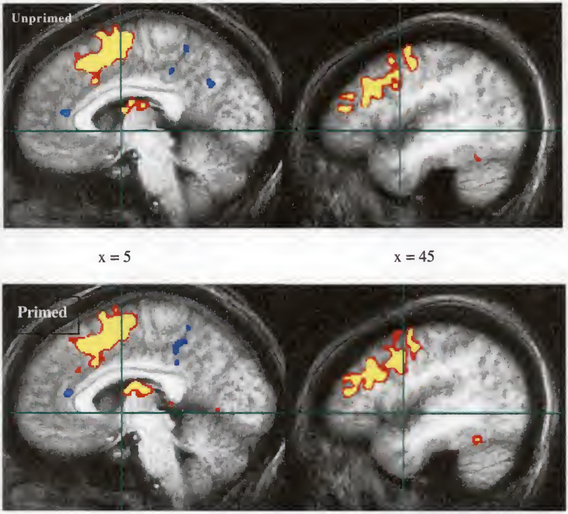
Priming

Eleven of the 28 scanned participants met criteria for inclusion in the priming analysis. Table 5 contains the magnitude of priming (percent targets for primed minus percent targets for unprimed categories) for the 11 participants who surpassed the 8.3% minimum magnitude of priming criteria discussed above. By applying a minimum magnitude of priming criteria, the strength of the behavioral priming effect ensures that the following FMRI analyses can not be criticized for a small behavioral effect.

Table 5. Magnitude of Priming (% targets in primed categories minus % targets in unprimed categories) for 11 Participants Who Showed Priming.

Subject #	Magnitude of Priming
21	10.2
23	16.9
25	21.7
34	19.1
37	12.3
38	27.1
39	25.9
41	10.8
45	16.8
46	13.3
52	11.7
Mean	16.9
SD	6.0

Figure 5 depicts group-averaged activation seen in the left hemisphere lateral and medial frontal cortex for both primed and unprimed CEG. Functional activity is overlaid



x = 5 x = 45

Figure 5. Medial (x = 5) and lateral (x = 45) left frontal activation during generation of unprimed (top row) and primed (bottom row) categories. Red and yellow represent task-related activation at $p < .001$ and $p < .0001$ respectively. Dark and light blue represent activation occurring during the rest period at $p < .001$ and $p < .0001$ respectively. The green crosshairs are located at the y and z origin (0, 0).

onto averaged anatomic scans across the 11 participants. The left medial frontal activation is very similar in both primed and unprimed CEG. It covers medial BAs 6 and 8, and it extends into medial BA 32. Most of the activation covers the region called "pre-SMA." (BAs 6 and 8 anterior to the vertical line arising from the anterior commissure), and some extends into paracingulate cortex (BA 32). It does not appear to involve BA

24, though the activation may touch on superior aspects of BA 24 (i.e., within the banks of the cingulate sulcus). These findings partially confirm Hypothesis 2. Tables 6 and 7

Table 6. Regions of Activation for the Primed and Unprimed CEG.

	Left Hemisphere	Right Hemisphere
Lateral Frontal		
motor/premotor	BA 6, 4	
Broca's area	BA 44, 45	BA 44, 45[b]
MFG	BA 8, 9, 46	BA 8, 9, BA 10[b]
Insula		Anterior Insula
Medial Frontal		
SMA	BA 6,	
paracingulate	BA 32	BA 32
pre-SMA	BA 6, 8	BA 6/8
Parietal		
parieto-occipital	deep parieto-occipital sulcus[a]	
post. cingulate		BA 29[a]
Subcortical		
Caudate Nucleus	Body of Caudate Nucleus	Body of Caudate Nucleus
Putamen		Putamen
Other Regions		
fusiform / cerebellum	Sup. Cerebellum, BA 37	
Inf. Temporal G	BA 21, inf temporal sulcus[a]	
Striate Cortex		BA 17[a]
Vermis of Cerebellum	Vermis	Vermis

[a]Activated during primed categories only
[b]Activated during unprimed categories only

contain a listing of regions of increased and decreased activation for the generation tasks. Regions of decreased activation (referred to as "deactivation" for simplicity) represent a greater average signal occurring during the rest period.

Figure 5 demonstrates that activation in left lateral frontal cortex is also highly similar between primed and unprimed CEG. The regions of increased activation and deactivation for primed and unprimed CEG are listed in Tables 6 through 10, including

Table 7. Regions of Deactivation for Primed and Unprimed CEG.

	Left Hemisphere	Right Hemisphere
Medial Frontal		
ant. cingulate	BA 32	BA 24, 32
MFG		BA 10
Parietal		
precuneus	BA 31 (small)	
post. cingulate/paracingulate	BA 23, 31,	BA 31
sup. parietal		BA 7
medial parietal	BA 7/5	BA 7
Temporal		
STG		BA 22
Inf. parietal	BA 39, 40	BA 39, 40
Subcortical		
Caudate Nucleus		Head of Caudate[b]

[a]Activated during primed categories only
[b]Activated during unprimed categories only

regions not shown in the figures. Across both tasks, activation involved premotor cortex extensively (BA 6), and the activation travels anteriorly across a substantial portion of the middle frontal gyrus, involving BAs 8, 9, and 46. Activity also extended into the gray matter in the inferior frontal sulcus beneath these cortical regions. Additional activation was seen on the inferior frontal gyrus in BAs 44 and 45, though this activation was less extensive than that seen on the middle frontal gyrus. These findings complete the predictions made in Hypothesis 2 and indicated that the word generation task activates regions similar to those in other language production studies.

Hypothesis 3 stated that CEG priming will result in decreases in activation in the regions of medial and lateral frontal cortex described above. When images obtained during primed CEG were compared directly to those obtained during unprimed CEG, there were no regions of activation that reached statistical threshold of $p < .001$. An analysis of individual volumes of activation in medial frontal cortex was conducted on an

exploratory basis to determine whether the group analysis was insensitive to subtle changes in activation patterns. Average volumes of left medial frontal activation for the 11 participants who showed priming are presented in Table 8. The difference in activated volumes was not significant ($t = -0.5$, $p > .3$). Therefore, Hypothesis 3(a) and 3(b) were not confirmed.

Table 8. Average Volumes of Activation (in microliters) in Medial Frontal Cortex for Primed Subjects.

	Primed	Unprimed
Mean	1137	1066
SD	788	736

Practice

Figure 6 depicts the results of the within-subjects ANOVA performed across the three levels of practice, and Table 9 contains the location and volumes of the activation areas. There were no significant differences between practice levels in medial or lateral frontal cortex. To determine whether the group analysis was insensitive to subtle changes in patterns of activation in medial and lateral frontal cortex, an analysis of individual volumes of activation in medial frontal cortex was conducted. Table 10 contains the average individual volumes of left medial frontal activation for the 26 participants. The difference between levels of practice was not statistically significant ($F = 0.88$, $p > .4$). Thus, Hypothesis 4 was not confirmed.

Instead, two other regions showed evidence of practice effects (see Table 9). The two main regions that showed practice effects were posterior cingulate cortex, which was

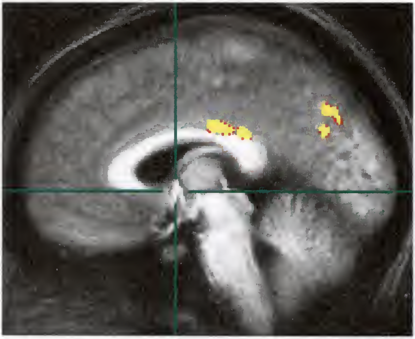


Figure 6. Practice effects as testing by within-subjects ANOVA. Red represents $p < .001$, while yellow represents $p < .0005$. Activation represents regions that differ between the three levels of practice.

specifically localized to BA 23, and medial parieto-occipital cortex, which was localized to the deep parieto-occipital sulcus in both hemispheres (touching on BAs 7 and 31) as well as BA 7 in the right hemisphere. Post-hoc t-tests are presented in Figure 7, including comparisons between the first and second practice runs and the first and third practice runs. There were no differences between the second and third practice runs (not shown). Since the second and third practice runs did not differ, and since comparisons between the first practice run and both the second and third practice run yielded significant activation differences, the significant ANOVA must be due to unique activity

Table 9. Regions of Significant Difference among Levels of Practice: ANOVA Results.

Region	Center of Mass[a]	Brodmann Area	Volume (microliters)[a]
Posterior Cingulate	2, -20, -30	right BA 23	508
	3, -32, -26		214
Medial Parietal	-1, -72, -39	left BA 7/31, right BA 7	493
Parieto-occipital sulcus	8, -68, -28	bilateral BA 7/31	474

[a]Based on atlas coordinates and Brodmann areas according to Talairach and Tournoux (1988)

Table 10. Average Volumes of Activation (in microliters) in Medial Frontal Cortex for Levels of Practice.

	Trial 1	Trial 2	Trial 3
Mean	1108	850	848
SD	850	729	864

during the first practice run. Figure 8 shows medial activation separated by the three levels of practice. The main difference between the first practice run and the subsequent runs is the significant lower activity level in posterior cingulate and medial parieto-occipital cortex that occurred solely during the first practice run. Recall that the first practice run was not only the first encounter with those categories but also occurred in the context of the priming phase, where those categories served as unprimed control categories and now serve as the first practice trials.

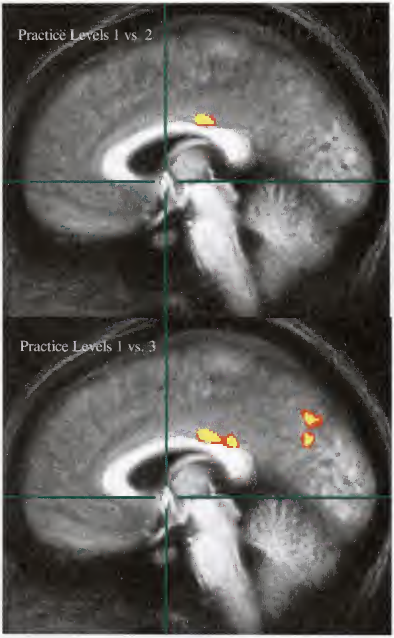


Figure 7. Post hoc t-tests comparing practice level 1 vs. level 2 and level 1 vs. level 3. Both red ($p < .001$) and yellow ($p < .0001$) represent higher average signal in levels 2 and 3 compared to level 1.

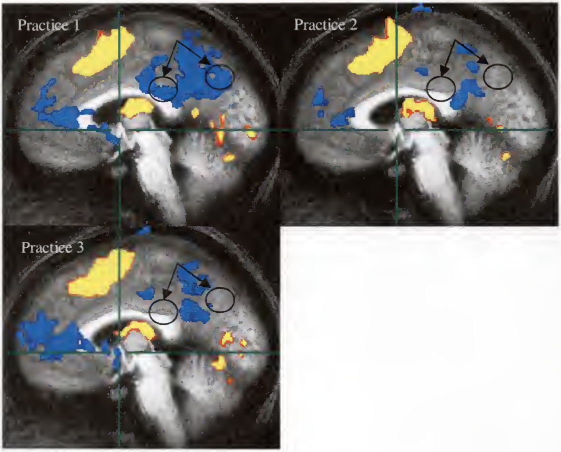


Figure 8. Post-hoc t-tests comparing the mean of each level of practice to a hypothetical mean of 0 (no activation at that level). Notice that there are many regions of common activation. Compare the circled regions to each other and to the regions of difference in Figures 4 and 3. This region represents the main effects of the ANOVA depicted in Figure 3 and indicates that the main effect is due to a lower level of activation in Practice level 1.

CHAPTER 7
GENERAL DISCUSSION

Priming

Previous functional neuroimaging studies of priming resulted in decreased acquired signal during priming tasks (e.g., Buckner et al, 1995, 1998; Demb et al., 1995; Blaxton et al., 1996). The present study observed no such effects using FMRI. It was hypothesized that CEG for primed categories would result in a smaller magnitude of FMRI BOLD effects compared to CEG for unprimed categories in both left medial and left lateral frontal cortex. The hypothesized decreases in left medial frontal cortex were proposed to be related to facilitation in the selection and production of previously accessed words. The hypothesized decreases in left lateral frontal cortex were proposed to be related to semantic processing. While activation was observed in both of these regions for primed and unprimed CEG alone, direct comparison of primed and unprimed CEG did not result in a significant difference.

One possible explanation for the lack of findings is that medial and lateral frontal cortex are not involved in semantic processing and response selection/production that were hypothesized to be subject to priming in CEG. While left medial frontal cortex is reliably involved in language production (Warburton et al., 1996; Crosson et al., 1999; Petersen et al., 1988), this region may not be susceptible to priming effects. It could be

that there is no transfer of processes between study and test for response selection and production, and, as a result, there is no reduction in medial frontal activation related to this cognitive process. Given that there are no prior functional neuroimaging studies of CEG priming, the context of the present findings is unclear and warrants further study. Methodological improvements are discussed below.

There are several studies related to lateral frontal cortex and semantic processing and priming, however, which do provide a context for the present findings of no frontal priming effects. Most published studies of functional neuroimaging have observed a decrease in activation in lateral frontal cortex related to conceptual priming (Wagner et al., 1997; Gabrieli et al., 1995; Demb et al., 1995; Buckner et al., 1995). However, studies of patients with frontal lobe lesions indicate that conceptual priming is intact despite left frontal lobe damage (Mimura, Goodglass, & Milberg, 1996; Milberg & Blumstein, 1981; Gershberg, 1997). Milberg's laboratory used a lexical decision task during which words were categorized faster if they were preceded by a semantic associate. Gershberg (1997) actually used a form of CEG priming in patients with left lateral frontal lesions and observed normal CEG priming in lesioned patients. Based on these findings, Gershberg has suggested that semantic processing may be sufficient to recruit frontal lobe activity in functional neuroimaging studies, but that left lateral frontal cortex may not be necessary for semantic processing. Otherwise, lesions to left lateral frontal cortex would result in deficits on priming tasks that rely on semantic processing. There are at least three methodological problems that must be resolved before it is concluded that left medial and left lateral frontal cortex are not involved in CEG priming: (a) small effect size; (b) the unknown effect of priming atypical exemplars; and (c)

procedural and other methodological differences from previous imaging studies of priming.

Small Effect Size

CEG priming resulted in a 10% to 27% increase in production of target items for primed categories compared to unprimed categories across participants in the selected subsample. Within this subsample, the amplitude of the priming effect is comparable to that seen in other CEG priming studies, indicating that the design employed here was similar in its behavioral effects within the selected subsample to the design in other studies (Keane et al., 1997; Gabrieli et al., 1995; Light & Anderson, 1989; Hamann, 1990). However, when this priming magnitude is considered in light of the total number of words that are produced for each category (six to 11 total words produced; means in Table 1), the rate of primed word production is less than one word for each category (priming magnitude is calculated by subtracting the number of targets produced in unprimed categories from the number of targets produced in primed categories). This estimate of the frequency of primed words is conservative, since it assumes that primed responses are those that occur beyond the base rate of target occurrence in unprimed CEG. Even so, the frequency of primed words is quite small compared to the total number of words produced. It seems highly possible that the occurrence of primed words was too infrequent to have an impact on the BOLD FMRI response. Previous functional neuroimaging studies of priming relied on a greater density of primed items within the imaged periods, thus resulting in more sensitivity to priming-related changes in cellular energy needs. Previous PET studies utilized a 50-75% target density (Buckner et al.,

1995; Squire et al., 1992), and previous FMRI studies utilized 100% target density (Wagner et al., 1997; Demb et al., 1995; Gabrieli et al., 1996; Buckner et al., 1998).

Priming of Atypical Exemplars

A second possible explanation for the lack of priming effects is that the priming of atypical category exemplars may have resulted in changes in threshold for activation that were different than for typical exemplars. It was assumed that CEG priming would affect all category exemplars similarly, regardless how typical the exemplar was or how likely a person would be to produce each particular item. In fact, Battig and Montague (1969) demonstrated that people tended to produce some exemplars before others. For example, within the category "flowers," their participants produced "rose" before "marigold." In terms of threshold for activation, it seems likely that "marigold" is at a lower resting threshold than "rose" and therefore less likely to be chosen as a response. When "marigold" is primed by some prior processing, its threshold may decrease only to the same level as "rose" rather than becoming easier to access than "rose." In terms of neural energy consumption, access to an atypical exemplar before priming, such as "marigold," may require more energy than for "rose" due to the additional requirements of accessing an exemplar that may be more "distant" from or more weakly associated with the semantic category. A hypothetical depiction of this hypothesis is contained in Figure 9. When an atypical exemplar is primed, the decrease in energy consumption to access the item may be relative to its own resting activation level rather than to other exemplars. Thus, if "marigold" is primed, its threshold for activation becomes equal to a more typical exemplar and is therefore indistinguishable from a threshold or from neural energy standpoint. The BOLD response may then appear as equivalent to that of more

typical exemplars and may not appear as a decrease in BOLD response as hypothesized (since the BOLD response in priming studies has been assumed to reflect some form of energy consumption or degree of neural efficiency).

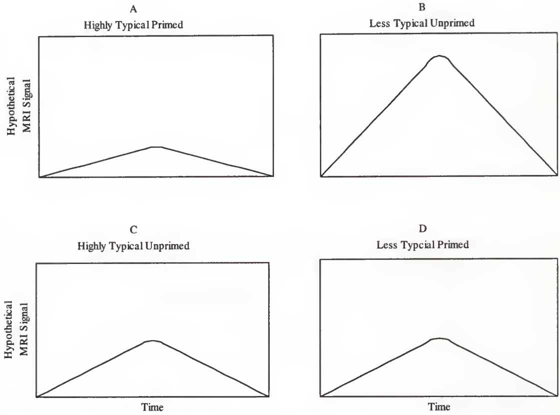


Figure 9. Hypothetical BOLD response to priming of highly typical versus less typical category exemplars. Less typical exemplars may require more energy for retrieval than highly typical exemplars in general, without priming, and therefore result in differences in baseline activation levels between accessing highly typical vs. less typical exemplars. (B vs. C). The lack of priming effects in the present study may be due to the possibility that priming of less typical category exemplars resulted in similar MRI signal compared to unprimed highly typical exemplar (C vs. D). Energy demands (presumably influencing BOLD response) between retrieval of primed atypical exemplars and unprimed typical exemplars is therefore similar and not detected in the present study.

<u>Other Methodological Differences</u>

Prior functional neuroimaging studies of priming used several techniques that may have provided extra facilitation for primed items and resulted in activation

differences that may be due to mechanisms other than priming. For example, Squire et al. (1992) and Buckner et al. (1995) required participants to study each word twice before priming was assessed with a word stem completion task. Buckner et al. (1998) had participants make semantic decisions about pictures six times in order to “maximize the likelihood of generating sufficiently robust reduction effects…” (p. 293). It is reasonable to question whether this study was truly a priming study or whether the extensive experience participants had with target items placed this study in the category of “practice” or skill acquisition studies (Schwartz & Hashtroudi, 1991). Reductions in activation observed in the above studies were interpreted as related to priming. Raichle et al. (1994) utilized a similar paradigm that involved nine exposures to each item, though he portrayed the mechanism to represent “practice.” The authors observed activation changes in both left medial and left lateral frontal/perisylvian cortex. Activation reductions in Squire et al. (1992), Buckner et al. (1995), and Buckner et al. (1998) may be due to practice rather than priming given the multiple exposures to each item in these studies and considering the findings of Raichle et al. (1994). Thus, the cortex in which activation reductions were observed may be associated not with priming but with practice.

In addition to the small effect size of CEG priming described above, the present CEG priming paradigm does not allow for the degree of experimental control over the timing of the occurrence of primed events as other methodologies that utilized single trials with only 1 response per trial. These studies used word stem completion (Squire et al., 1992; Buckner et al., 1995), word fragment completion (Blaxton et al., 1996), or semantic or perceptual classification of words or pictures (Wagner et al., 1997; Demb et

al., 1995; Buckner et al., 1998). In these studies, the occurrence of target items was more predictable and thus enhanced the chances of observing changes in patterns of brain activation.

Another possible explanation for the lack of priming effects in medial and lateral frontal cortex is that there was contamination by perceptual processes that may have reduced the magnitude of conceptual processing during priming. Recall that the study task involved a phonemic cue (e.g., "whiskers - /ka/;" see Figure 2). Ellis and Young (1988) have proposed that the input and output phonological lexicons are bi-directionally connected (Figure 1), such that activation of a lexical unit in the phonological input lexicon may result in activation of the same unit in the phonological output lexicon. This perceptual processing related to the phonemic cue may have influenced the response during study as much as the conceptual priming, thereby diluting the conceptual priming effects. There is no evidence to date that suggests perceptual priming would interfere with conceptual priming in this fashion, indicating that this hypothesis would require further exploration.

With these methodological issues in mind, there is one important way the present design could be improved to enhance the likelihood of detecting priming. An event-related paradigm of CEG priming may resolve most of the issues discussed above. Event-related paradigms, such as that used by Buckner et al. (1998), provide the ability to select only those trials for which a target item was produced and priming presumable occurred, thus ensuring that the acquired signal is free from noise introduced by blocking both primed and unprimed trials together and attempting to bias the activation patterns with a majority of one type of trial. An event-related approach would not only reduce the

impact of the small effect size problem, but also it would increase control over the temporal resolution of the priming phenomenon and therefore increase the likelihood of detecting priming effects on FMRI signal. It is also possible with an event-related approach to separate highly typical and less typical exemplars and compare relative changes in activation response between levels of typicality. For example, images obtained during priming of highly typical exemplars could be compared to images obtained during priming of less typical exemplars to detect signal differences. An appropriate control condition would compare analogous images obtained during unprimed production of highly typical and less typical exemplars.

Practice

It was hypothesized that the repeated generation of category exemplars for the same categories would result in a decrease in activation in left medial frontal cortex but an increase in left inferior lateral frontal cortex as observed by Raichle et al. (1994). Decreased left medial frontal activation was proposed to be attributable to the decreased amount of energy required for selection and production of rehearsed responses. Increased left lateral inferior frontal cortical activation was proposed to be attributable to the function of that region in supporting automatic processing. However, neither of these hypotheses was confirmed in the present study. Instead, different regions of medial cortex were observed to change with practice, including posterior cingulate cortex and medial parieto-occipital cortex.

The lack of practice-related activation changes in left medial and lateral cortex may be due to insufficient practice of the generation task. Raichle and colleagues (1994) had participants engage in 10 practice trials of their verb generation task, which was

substantially more than was conducted in this study. It could be argued that a few practice trials should be sufficient since studies of priming show activation changes with as few as one or two repetitions (e.g., Gabrieli et al., 1996; Demb et al., 1995). However, each of those studies utilized a task for which there was only one response for each stimulus, and the responses were more predictable and more consistent than those in category exemplar generation. In a recent study of practice-related changes in activation patterns, Buckner et al. (2000) observed no medial frontal changes after participants engaged in four practice trials of word stem completion and verb generation. As in the present study, a small number of practice trials was insufficient to produce observable activation changes in medial frontal cortex. One possibility is that activation changes in medial frontal cortex may occur somewhere between 4 and 10 practice trials. However, Buckner et al. (2000) did observe activation changes in left inferior lateral frontal cortex and left inferior temporal cortex after only four practice trials. This suggests that different areas of cortex may be affected by different amounts of practice. Further research into the amount of practice sufficient to produce medial frontal activation changes in CEG is required to answer this question.

While the hypothesized changes in left medal and lateral frontal activation were not observed, practice effects were observed in two regions, including the left posterior cingulate cortex (BA 23) and bilateral medial parieto-occipital cortex in the region of the parieto-occipital sulcus (BAs 7 and/or 31). These regions demonstrated a greater degree of deactivation (i.e., a rest-related increase in signal) during the first practice run only (Figure 8). Deactivation in the medial parieto-occipital region has been reliably observed in tasks that utilize a visual fixation point as a control task (e.g., Ojemann et al., 1998;

Warburton et al., 1996; see Shulman et al., 1997 for a review of deactivations). The deactivation in medial parieto-occipital cortex during the first practice generation categories is most likely due to attention to the visual fixation point during the rest period. Two hypotheses can explain changes in rest-related activation as CEG is practiced. First, it is possible that as the task becomes more automatic, and externally focused attention increases during the generation periods and becomes equal to that in the rest period. This hypothesis is supported by subjective observation of our data, which revealed that there was frequent eye movement during the generation periods consistent with less focus on the external fixation point. As CEG becomes more automatic, eye movements may become less frequent and the focus on the fixation point may increase, resulting in similar levels of externally focused attention during the generation periods relative to the rest periods. This increase in externally focused attention during generation is reflected by the lack of activation difference between rest and generation in the second and third practice levels (Figure 8). Conversely, participants may become less externally focused during the rest periods as practice progresses, which can be characterized as a form of habituation to the fixation point. As the entire task becomes more familiar, participants are less externally focused during the rest periods. This rest-related decrease in external focus is reflected by the lack of activation difference between rest and generation in the second and third practice trials seen in Figure 8. Nadeau et al. (1997) observed increases in posterior medial activation with a visual stimulation task relative to eyes closed rest period, supporting the role of medial posterior cortex in externally focused attentional processes. Both of these competing hypotheses are consistent with the general hypothesis that a shift from internally-guided to externally-

guided attentional states may explain practice-related change in posterior medial activation.

Posterior cingulate deactivation followed the same pattern as medial parieto-occipital activation: an increase in deactivation during the first practice level was responsible for the practice-related changes in this region. While it is well known that the anterior cingulate region is frequently involved in tasks assessing language, memory and attention (see Cabeza & Nyberg, 2000 for a review), posterior cingulate activation is far less common. However, a few studies have found that posterior cingulate activation can occur with visual attentional processing as well (Corbetta et al., 1993; Bench et al., 1993; Andreasen et al., 1996). It is possible that the posterior cingulate and parieto-occipital regions form a system related to visual attention. In fact, it appears that posterior cingulate activation in studies of attention typically co-occurs with parietal activation, further supporting that these two regions form a network of visual attention (Cabeza & Nyberg, 2000). As the attentional states changed from internally-guided to externally-guided, so did activity in attention-related cortex. Of course, eye movements should be explicitly monitored in future research to test this hypothesis.

The lack of left medial and left lateral activation changes associated with CEG priming and CEG practice suggest a general problem with this paradigm, which is that there is poor control of the cognitive processes involved in this task. While some cognitive processes engaged by the task are certain, including the self-guided initiative to perform the task and the semantic nature of the task, other cognitive processes engaged by the task are less certain, such as the rate of production across the generation periods, the exact strategy used by each subject (e.g., some participants may visualize items in the

category, while some may use the alphabet as a guide), and exactly which items are produced reliably between each participant. Highly educated people may produce more items in obscure categories (e.g., types of metal – "sodium"). These are only a few examples of the variability in responses that can be expected between participants. Some researchers have utilized creative methods around some of these problems, such as Keane's use of a baseline established for each participant individually for category generation (Keane et al., 1997). Since participants could not speak out loud during the FMRI phase, little is known about their actual responses, and therefore little can be said about their individual strategies. Once again, an event-related approach would allow audible responses and enhance the degree of control over the task (Birn et al., 1999).

In summary, it seems that subtle behavioral changes can be difficult to measure in the functional neuroimaging environment. Studies that have taken extra steps to bolster their behavioral effects have shown stronger functional imaging effects. In turn, these studies may also have sacrificed their initial goal of measuring a subtle cognitive effect for a robust activation effect. Development of new functional imaging paradigms, such as single event FMRI, will hopefully allow for the imaging of subtle cognitive effects without sacrificing sensitivity to small changes in brain activation.

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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